# EXHIBIT 1
# Part 3 of 3

In addition, Amgen argued against suspending prosecution during the co-pending *Fritsch v. Lin* interferences No. 102,096 (Fritsch I) involving the Lin '008 patent and No. 102,097 (Fritsch II) involving the Lin '179 process application, in view of the December 11, 1989 decision in *Amgen, Inc., v. Chugai Pharm. Co., Ltd. and Genetics Instit., Inc.* Civil Action No. 87-2617-Y. In particular, Amgen indicated that against an anticipation attack based on Dr. Fritsch's work at Genetics Institute, not only had the Court upheld claims of the Lin '008 patent directed to the purified and isolated DNA sequence for human erythropoietin, it had also upheld claims to a host cell transformed with such a sequence. (AM-ITC 00941216-17). Amgen also asserted the Court's decision was therefore "fully dispositive" not only of any priority issue in both interferences, including the Fritsch II interference involving the '179 application, but also of any priority issue in the subject '178 application, stating: "if Lin was the first to invent the DNA encoding erythropoietin and the use of that DNA in a host cell to produce recombinant erythropoietin, then clearly he was the first to invent a recombinant erythropoietin product produced using such a host cell." (AM-ITC 00941217). Knowing this, Amgen again knowingly and intentionally failed to disclose the rejection by Examiner Tanenholtz as to the obviousness of the process -- a patentability issue which was not decided by the Court or the Board of Patent Appeals and Interferences -- while at the same time arguing that its amendment rendered the claims "in condition for immediate allowance and issuance of a patent." (AM-ITC 00941216).

Amgen continued prosecution of the '178 claims in the '874 application, which Amgen filed on February 28, 1994 (AM-ITC 00941417). As discussed above, Mr. Borun submitted a voluminous Information Disclosure Statement ("IDS"), listing 394 references, including purported "references of record" in the parent applications of the Ser. No. 113,178, Ser. No. 113,179, the European Opposition Proceeding involving Amgen's EP 148,605 and defendant's

section 282 notice from *Amgen v. Chugai*, as well as admitted exhibits from *Amgen v. Chugai*. (AM-ITC 00941422-49). Significantly, a biotechnology examiner would only have spent approximately 20 hours examining any individual application, such as the '874 application. (*See, e.g.*, U.S. Gen. Accounting Office, GAO-RCED-89-120BR, Biotechnology, Backlog of Patent Applications, at 20 (1989)). Although the IDS included the Yokota and Gething references cited in the '179 prosecution by Examiner Tanenholtz, those references were effectively buried because (1) the known relevance of the references had been omitted by Amgen and (2) had the examiner devoted all his time merely to reviewing the cited references, he would have had only about three minutes for each reference. The continued failure to bring the rejection by Exminer Tanenholtz to the attention of the examiners in the '178 line of applications, or to point out the relevance of the Yokota and Gething references to that rejection, assured that the material nature of these references would remain buried under a mountain of other art.

Amgen's failure to disclose relevant rejections from its co-pending '179 line continued still in its prosecution of the '874 application. In a Preliminary Amendment (AM-ITC 00941452-54), Amgen cancelled all pending claims, which it replaced with new claims 84-89 (which going forward were renumbered as claims 87-97). Among the new pending independent claims, Amgen again included product-by-process claims defining the claimed human erythropoietin glycoprotein solely through the process by which it was produced. For example, claim 86 (renumbered as 89) recited:

> The *in vivo* biologically active human erythropoietin glycoprotein product of the process comprising the steps of:
>
> > (a) growing, under suitable nutrient conditions, ***mammalian host cells transformed or transfected with an isolated DNA sequence*** encoding the human erythropoietin amino acid sequence set out in FIG 6 or a fragment thereof; and
> >
> > (b) isolating a glycosylated erythropoietin polypeptide therefrom.

(AM-ITC 00947453). Amgen again failed to raise the August 1988 rejection by Tanenholtz that the process of host cell expression incorporated into this claim would have been obvious over Yokota and Gething.

Subsequently, Amgen filed Ser. No. 468,556, which ultimately issued as the '080 patent, as well as application Ser. No. 487,774, which ultimately issued as the '933 patent, as continuation applications from the '874 application. Amgen's failure to disclose the highly relevant and material rejections it received during the '179 prosecution, as described herein, during prosecution of the '178 and '874 applications, therefore critically tainted the prosecution of both the '080 and '933 patents. Accordingly, on these grounds, both the '080 and '933 patents should be held unenforceable for inequitable conduct before the Patent Office.

Amgen's pattern of intentionally withholding material information from the various examiners is further evidenced by its failure conversely to disclose rejections it received in the course of prosecuting claims in the '178 line of applications during its prosecution of the '179 application as well as in further continuations of the '179 application, specifically, application Ser. No. 609,741, Ser. No. 957,073, and Ser. No. 100,197. The '178 application contained pharmaceutical composition claims that were substantially similar to those of the '741, '073 and '197 applications, which eventually issued as the '422 patent. In addition, as discussed above, the '178 application contained product-by-process claims that were substantially similar to the process claims of the '179 application, which eventually issued as the '868 patent.

In particular, during the prosecution of substantially similar claims in the '179, '741, '073 and '197 applications, Amgen failed to disclose the following rejections made during the prosecution of the '178 application:

- The June 2, 1988 rejection by Examiner Kushan rejecting, among others, claim 55 ("A pharmaceutical composition comprising an effective amount of a polypeptide according to

claims 1, 16, 39, 40 or 41.") under 35 U.S.C. 103 as being unpatentable over Miyake *et al.*, Takezawa *et al.*, Chiba *et al.* or Sugimoto *et al.* in view of Papayannopoulo *et al.* (AM-ITC 00941098). Examiner Kushan concluded that "Each of the primary references above would enable one of ordinary skill in the art to prepare biologically active, homogenous human EPO." (AM-ITC 00941098). Nonetheless, Amgen argued for the patentability of claims substantially similar to rejected claim 55 in the '741, '073 and '197 applications and failed to disclose the prior rejection by Examiner Kushan. (AM-ITC 00899084; AM-ITC00899123-27; AM-ITC 00899151-54);

- The February 10, 1989 rejection by Examiner Kushan rejecting, among others, claims 61-66 ("61. A glycoprotein product according to claim 41 further characterized by being the product of expression of an exogenous DNA sequence in a eucaryotic host cell.") under 35 U.S.C. §103 as being unpatentable over Miyake *et al.*, Chiba *et al.*, Takezawa *et al.* or Sugimoto *et al.* and claims 55 and 61-66 under 35 U.S.C. 103 as being unpatentable over Miyake *et al.*, Chiba *et al.*, Takezawa *et al.* or Sugimoto *et al.*, in view of Papayannaopoulo *et al.* (AM-ITC 0094115057). Amgen argued for the patentability of claims substantially similar to the rejected claims in the '179, '741, '073 and '197 applications and again failed to disclose the prior rejections by Examiner Kushan. (AM-ITC 00899084; AM-ITC00899123-27; AM-ITC 00899151-54; and AM-ITC 0095320709, AM-ITC 00953638-39);
- The June 20, 1989 rejection by Examiner Kushan rejecting, among others, claims 67-73 under 1) the doctrine of obviousness-type double patenting as being unpatentable over the prior invention as set forth in claim 1 to 11 of U.S. Patent No. 4,667,016, 2) 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Sugimoto et al. and 3) 35 U.S.C. 103 as unpatentable over Sugimoto et al. in view of Papayannopoulo et al. Amgen argued for the patentability of claims substantially similar to the rejected claims in the '179, '741, '073 and '197 applications and again failed to disclose the prior rejection by Examiner Kushan. (AM-ITC 00899084; AM-ITC00899123-27; AM-ITC 00899151-54; AM-ITC 0095320709, AM-ITC 00953638-39; AM-ITC 00953205-25; AM-ITC 00953637-48);
- The September 18, 1989 rejection by Examiner Kushan rejecting, among others, claims 67-73 under the doctrine of obviousness-type double patenting as being unpatentable over the prior invention as set forth in claim 1 to 11 of U.S. Patent No. 4,667,016. Amgen argued for the patentability of claims substantially similar to the rejected claims in the '179, '741, '073 and '197 applications and again failed to disclose the prior rejection by Examiner Kushan. (AM-ITC 00899084; AM-ITC00899123-27; AM-ITC 00899151-54; AM-ITC 0095320709, AM-ITC 00953638-39; AM-ITC 00953205-25; AM-ITC 00953637-48).

Accordingly, each of the patents-in-suit is unenforceable for inequitable conduct.

**Amgen Concealed The Standard Used In RIA From The Examiner**

U.S. 5,756,349 ("the '349 patent") issued on May 26, 1998 from Ser. No. 08/468,369 ("the '369 application"). Like the other patents-in-suit, the '349 patent was filed through a chain of continuation and continuation-in-art applications dating back to December 13, 1983. Each

and every claim of the '349 patent requires measurement of cells grown in culture in excess of a specified amount as "U of erythropoietin per $10^6$ cells in 48 hours as determined by radioimmunoassay" (known as "RIA"). ('349 patent, claims 1-7, col. 10:40-47).

Example 2 of the '349 patent sets forth part of the protocol for conducting the radioimmunoassay; however, the protocol discloses only "an erythropoietin standard" and not the standard used by Dr. Lin and his colleagues in developing his "invention." (Compare '349 patent, col. 16:39-4 with AM-ITC 00551000; 3/27/07 Egrie Depo. Tr. 194-195)). Example 10 further sets forth experimental results using RIA to determine "effective production rates" as "U of erythropoietin per $10^6$ cells in 48 hours" ('349 patent, col. 26:33-52), again omitting the standard used to conduct the RIA.

Dr. Egrie developed the radioimmunoassay used by Amgen to evaluate recombinant erythropoietin. (3/27/07 Egrie Depo. Tr. 106-107). Dr. Lin relied on the RIA protocol and associated test results to demonstrate that his disclosed vertebrate cells met the claim limitations of the '349 patent. (3/28/07 Lin Depo. Tr. 162-163). In that protocol, Dr. Egrie used CAT-1 urinary EPO as the assay standard (3/27/07 Egrie Depo. Tr. 194-195), and not the standard International Reference Standard. (3/27/07 Egrie Depo. Tr. R. 45, 52-53, 134-136, 172, 183-184; AM-ITC 00550777 ("In most other papers, (i.e. Garcia-1979, 1982, Rege-1982, Biregard-1982) EPO titration of sera or plasma on RIA was done against WHO#2IRP.")). Different urinary erythropoietins were available for use (3/27/07 Egrie Depo. Tr. R. 160-163, 169-170, 184; AM-ITC 00061675; AM-ITC 00550986; AM-ITC00551040), however, depending upon which one was chosen as a standard, different results would be obtained in RIA. (AM-ITC 00550986; 3/27/07 Egrie Depo. Tr. 187-188).

Additionally, as of September 1984, before the last CIP application was filed upon with the '349 patent is based, CAT-1 was no longer available from the National Institutes of Health (NIH) or Dr. Goldwasser -- the two sources for Amgen's standard. (AM-ITC 00061675-706 at AM-ITC 00061678; 3/27/07 Egrie Depo. Tr. 173-174). Likewise, the apparent replacement standard, Lot 82, was not disclosed or available to the public because it was an internal Kirin-Amgen creation.

Furthermore, Amgen's units do not equate to accepted international units, and are instead arbitrary units. (AM-ITC 00558618; 3/27/07 Egrie Depo. Tr. 191-192). The patent specification omits this fact. As late as 1990, Amgen's CEO, Dr. Rathmann acknowledged that Amgen "should be absolutely fastidious in reporting specific activity in arbitrary (Amgen) units until we can establish an excellent correlation with international units. I do not believe such correlation exists today ... I think we have also been careless with respect to what is the precision or uncertainty (accuracy) of our data ... I think we should understand how any standard can deviate from 'parallelism' trying to relate to international units." (Id.).

None of this information was disclosed to the examiner(s) of the applications leading to the '349 patent.

Accordingly, Amgen, including at least Dr. Lin, Dr. Egrie and Mr. Borun knew, or at a minimum should have known, that the claims being prosecuted were not patentable under at least §112, ¶1 and ¶2. Nonetheless, Amgen pressed ahead causing issuance of the claims. Moreover, the best mode for practicing the claims of the '349 was concealed from the examiner. This is particularly egregious because an examiner has no way of determining whether the best mode requirement for patentability is met without disclosure from the applicant. Likewise, because Dr. Egrie was intimately involved in developing and conducting the RIA assays disclosed in the

patent, the question of proper inventorship would have been important to the examiner in determining patentability of the claims. Accordingly, the '349 patent is unenforceable for inequitable conduct.

**Amgen Failed to Disclose Its Work With the 1411 Cell Line and Misrepresented the Art**

Lin Application Ser. No. 06/675,298 ("the '298 application") issued as US 4,703,008 on October 27, 1987, and is a parent to each of the patents-in-suit. When the '298 application was pending, the examiner rejected claims over the prior art for obviousness under §103.

Examiner Tanenhotz noted that "Ullrich et al and Martial teach a basic process for isolating mRNA and converting it into a cDNA library for use in cloning and expressing mammalian genes. It would be obvious to prepare erythropoietin as a fused peptide by extracting the messenger RNA for erythropoietin from kidney cells known to be rich therein and converting that mRNA to a cDNA library in the manner taught by Ullrich et al or Martial." (AM-ITC 00873694-95).

In arguing patentability over the rejection, Mr. Borun stated that:

> Thus, as pointed out in Applicant's submission of October 3, 1986, ***there was, at the time of the invention, a serious problem securing what could be recognized as erythropoietin-producing cells, much less cells producing high levels of the protein or cells "known to be rich" in erythropoietin messenger RNA*** such as would provide a cDNA library with multiple copies of erythropoietin-encoding DNA.
>
> For the Examiner to characterize the publications of Ullrich et al. and Martial et al. as readily enabling the preparation of a library including translatable human erythropoietin cDNA by an ordinarily skilled worker is unsupported and in fact contradicted by other references comprising the totality of the art.

(AM-ITC 00873748 (emphasis added).

In response to Mr. Borun's statements, Examiner Tanenholtz allowed all the pending claims. (AM-ITC 00873752; AM-ITC 00873752).

Mr. Borun, Amgen's in-house attorneys and those individuals involved with the '298 application, including Dr. Egrie, however, misrepresented and omitted important information that cells producing human erythropoietin existed. Indeed, Amgen and Dr. Egrie were provided supernatant from Dr. Gaylis which showed he had cells (1411H or yolk sac carcinoma cells) which produced significant amounts of erythropoietin over a prolonged period of time. (3/27/07 Egrie Depo. Tr. 270-280; AM-ITC 00052045; AM-ITC 00057704; AM-ITC 00057723; AM-ITC 00057735; AM-ITC 00057708-18, AM-ITC 0057689-701 (Egrie as co-author); AM-ITC 00057687; AM-ITC 00057688).

Likewise, Amgen's consultant on the erythropoietin project, Dr. Goldwasser, who also was involved with the drafting of the patents in suit was also provided supernatant to run assays in early 1983. (FG 000012-13 ("Subsequently we found that the cells produce significant quantities of Erythropoieitn (Ep). The erythropoietin activity was determined by the ability of the supernatant obtained from cultures of 1411H to: 1) Stimulate and sustain the formation of erythroid colonies by adult sheep marrow Colony Forming Unit - Erythroids. 2) Stimulate erythropoesis in ex-hypoxic polycythemic mice."); AM-ITC 00057687; AM-ITC 00057708-18 ("We wish to thank Dr. Eugene Goldwasser and Amgen for performing the radioimmunoassays."); see also FG 000014-21; FG 000048).

Moreover, published literature related to the cells plainly supported the examiners argument regarding obviousness. (Gaylis *et al.*, "In Vitro Models of Human Testicular Germ-Cell Tumors", *World J. Urol.*, 2:2-5 (1984) ("We recently detected production of significant amounts of erythropoietin (Ep) by a cell line designated 1411H ... Clearly, then, the production of Ep by 1411H is of significant biological interest and may be of clinical value if the gene controlling Ep synthesis can be cloned."); see also AM-ITC 00057739 and FG 000051 Ascensao

*et al.*, "Inducible Production of Erythropoietin by a Human Yolk Sac Tumor Cell Line", *Am. Fed. Clin. Res.* 31:307A (1983) ("We have identified a human yolk sac tumor-derived cell line (1411H) which can be induced to produce significant amounts of Ep."); Ascensao *et al.*, "Erythropoietin Production by a Human Testicular Germ Cell Line", *Blood* 62(5):1132-34 (1983) ("We have identified a human testis germ cell line 1411-H, that produces significant amounts of Ep. The erythropoietic activity was demonstrated by the ability of cell-free supernatants to stimulate erythropoiesis in exhypoxic polycythemic mice.")).

Amgen's inequitable conduct in securing the '008 claims infects all the patents-in-suit, rendering each unenforceable.

No individual affiliated with Roche, other than counsel, furnished information or is "most knowledgeable regarding the subject matter of this Interrogatory."

Roche expressly reserves the right to amend and/or supplement its interrogatory response as fact discovery and expert discovery progresses (including the availability of finalized deposition transcripts with errata).

**SECOND SUPPLEMENTAL RESPONSE TO INTERROGATORY NO. 26:**

Roche hereby incorporates by reference the information set forth in the April 6, 2007 Expert Reports of Michael Sofocleous, Charles G. Zaroulis, Ph.D., John Lowe, M.D., Rodney E. Kellems, Ph.D, Bruce Spinowitz, M.D. and Carolyn Bertozzi, Ph.D and the May 1, 2007 Supplemental Expert Reports of Michael Sofocleous, Bruce Spinowitz, M.D and Richard A. Flavell, Ph.D, and the respective accompany exhibits and demonstratives. In addition:

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

Amgen filed United States Application Serial No. 07/609,741 ("the '741 application" entitled "Production of Erythropoietin" which eventually led to the '422 patent for the purposes

of requesting an interference with claims 1-4 of U.S. Patent No. 4,879,272 (Shimoda *et al.*, assigned to Chugai) and "to protect the current clinical formulation of Epogen(R), containing human serum albumin." ('741 File History, Paper 2; 11/6/90 Preliminary Amendment; AM-ITC 00097004 - AM-ITC 00097018 at 005; also at AM-ITC 00097006). Subsequently, Amgen also attempted to provoke an interference with U.S. 4,806,524 (Kawaguchi *et al.*, assigned to Chugai).

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." ('741 File History, Paper 2, 11/6/90 Preliminary Amendment at 9-10; Paper 3 Examiner Interview Summary Record). The proposed count for the interference that Applicant attempted to provoke with the Kawaguchi '524 patent was: "An erythropoietin preparation containing one or more selected from the group consisting of bovine serum albumin, human serum albumin and gelatin." ('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 in both interferences. ('197 File History, Paper 2, 11/6/90 Preliminary Amendment at 9; Paper 18, 12/20/23 Amendment at 2).

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 at al., 1977 (R), Takezawa at al., 1981 (B) or Takezawa at al., 1982 (C) in view of either applicant's admission on page 87, fines 29-31 or Bock at al.. 1982 (D).
>
> ***The claims under instant consideration are drawn towards pharmaceutical compositions comprising erythropoietin in combination with human serum albumin.***
>
> Miyake at al. disclose the purification of human erythropoietin derived from human urine (see e.g. Abstract, section entitled "Experimental Procedures" and Table V). Miyake at

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 at 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 at 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 at al., 1982 (D) teach that human serum albumin (HSA) was a known and recognized pharmaceutical carrier and that the carder 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 during his search for prior art he had not discovered a reference that expressly disclosed a composition of erythropoietin comprising human serum albumin.

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

<u>The 35 USC §103 Rejections</u>:

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)). 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." (*See* '197 File History, Paper 32, 4/21/99 Examiner Interview; Paper 33, 4/28/99 Amendment at 5).

In light of Amgen's acknowledged motivation for filing the '741 application and prosecuting the '422 patent to issuance, it is clear that Amgen and those substantively involved in prosecuting the '741 application, including Mr. Odre and Mr. Watt, were highly motivated to obtain patent protection through whatever means necessary, including deliberately misleading the PTO by withholding highly material prior art.

In connection with the '741 application filing, Amgen conducted a search for the prior art, including scientific literature, patents, and other documents which included: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. 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) directed the search and others at Amgen who were substantively involved in the prosecution of the patents-in-suit, Jeffrey Browne, Joan Egrie and Thomas Strickland were all aware of the search (AM-ITC 00097004 - AM-ITC 00097018 at 006.)

A memo dated November 1, 1990, to Steven Odre and listing Jeffrey Browne, Joan Egrie and Thomas Strickland as recipients 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 (emphasis added); *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.")).

As further reported in the November 1 memo:

> ***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-AM-ITC 00097011 (emphasis added)).

Thus, Amgen, including at least Mr. Odre and Mr. Watt, in addition to the other recipients of the November 1 memo, were well aware of prior art describing the use of HSA or BSA (bovine serum albumin) in combination with erythropoietin and that such compositions of erythropoietin and HSA were disclosed in the prior art. (AM-ITC 00097005).

Aware of this highly relevant prior art, Amgen nonetheless filed the '178 application on November 6, 1990 and failed to disclose *any* of the prior art reported in the November 1 memo until over eight years later. Only then did Amgen disclose any of this art and in doing so, selectively disclosed only certain references while, knowingly withholding certain highly material references. Tellingly, Amgen chose to disclose only those references which according to the November 1 memo taught HSA or BSA as a carrier for erythropoietin in RIA or for

extraction and characterization of erythropoietin, and BSA and erythropoietin for use in animals. Deliberately omitted were any of the references disclosing the use of erythropoietin and HSA in humans or other animals or the use of erythropoietin and BSA in humans.

Specifically, in an Information Disclosure Statement submitted during prosecution of the '422 patent, Amgen failed to 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, but not the Baron-Goldwasser clinical study. Likewise, Applicant disclosed 3 articles by Garcia, but not the 1971 article uncovered by the literature search requested by Mr. Odre and reported in the November 1 memo.

During prosecution of the '422 patent in traversing rejections over the prior art, Amgen asserted that he improperly applied hindsight to combine references disclosing urinary erythropoietin (Miyake and Takezawa) with references generally suggesting the use of HSA in pharmaceutical preparations (Bock), and that the cited prior art failed to teach a pharmaceutically acceptable preparation or suggest that "BSA or other stabilizing additive would be necessary once the purified EPO was obtained." ('197 File History, Paper 23, 12/1/94 Request for Reconsideration at 3-4; *see also* Paper 33, 4/28/99 Amendment (Two other 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."). Amgen's failure to disclose highly material references identified in the November 1, 1990 memo is particularly egregious in light of these arguments made by Amgen.

As confirmed by the November 1, 1990 memorandum, the Baron-Goldwasser clinical study would have been important to a reasonable examiner examining claims 1 and 2 of the '422 patent and but for Amgen's failure to submit the information, the '422 patent would not have

issued. Similarly, the 1971 Garcia journal article would have been important to a reasonable examiner and had Amgen disclosed it, the '422 patent would not have issued.

Motivated by the need to protect the current clinical formulation of Epogen® containing human serum albumin by starting an interference, Amgen, including Mr. Odre and Mr. Watt had much to gain by withholding these highly material references in order to mislead the PTO and obtain patent protection. A number of individuals at Amgen who were substantively involved with the prosecution of the patents-in-suit, including the legal department through Mr. Odre, knew of these reference yet failed to disclose the information during the lengthy pendency of the '422 patent. Accordingly, the duty of disclosure and the duty of candor was violated in prosecuting the '422 patent to issuance.

This highly material information withheld during the prosecution of the '422 patent would have also been important to a reasonable examiner regarding the patentability of claims 9 and 12 of the '933, which are product-by-process claims. ('178 File History, Paper 11, 6/2/89 Amendment at 3). Claims 9 and 12 both depend from independent claim 3 (as well as others). Likewise, the information would have been important to a reasonable examiner regarding the patentability of claim 4 of the '080 patent.

Amgen and those substantively involved in prosecuting the '933 patent and the '080 patent would have known that if the product claimed in this manner 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 and, therefore, knew or should have known that the Baron-Goldwasser clinical study and 1971 Garcia article would have been important to a reasonable examiner.

The information in the November 1, 1990 memorandum, in addition to other information regarding the Baron-Goldwasser discussed in Roche's Supplemental Interrogatory response and the April 2 Expert Reports of Michael Sofocleous and Bruce Spinowitz, was known to the same individuals at the time the '933 patent and '080 patent claims were pending. Amgen (including Mr. Odre) was aware of the November 1 memorandum and knowing that the prior art disclosed compositions of erythropoietin and HSA (and BSA), nonetheless 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).

Despite its clear materiality, at no time during the prosecution of the '933 patent or the '080 patent did Amgen disclose any of the Baron-Goldwasser clinical study documents or the 1971 Garcia article. (See '874 File History, Paper 36, 4/8/94 IDS and PTO-1449 Form; '933 Patent, References Cited; '556 File History, Paper 7, 12/20/96 IDS and PTO-1449; '080 Patent, References Cited). Accordingly, Applicant violated the duty of disclosure and the duty of candor during the prosecution of the '933 and '080 patents. Additionally, the inequitable conduct that occurred in prosecuting the '933 patent infects the '080 patent, which claims priority to and is terminally disclaimed over the '933.

Submission of Dr. Goldwasser's testimony before the United States International Trade Commission (Investigation No. 337-TA-281 before Judge Harris) does not constitute 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. Similarly, 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)) failed to disclose the nature of the composition was used in the Baron-Goldwasser clinical study, i.e. human erythropoietin and human serum albumin. The selected portions of Dr. Goldwasser's testimony that were submitted contained only conclusory statements that insufficient amounts of erythropoietin were available to generate "any result." (e.g. AM-ITC 00849306-341 at AM-ITC 00849307; AM-ITC 00245727-29 at AM-ITC 00245728). This testimony contradicts statements made by Dr. Goldwasser and Dr. Baron to the U.S. Public Health Service and the FDA, 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. Amgen was aware of these contradictions.

Dr. Goldwasser's testimony in Judge Harris' opinion that was submitted to Patent Office does not 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 disclose the erythropoietin and human serum albumin composition used in the Baron-Goldwasser study or the patient data discussed above.

Submission of Judge Harris' opinion during prosecution of 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) would not have made the '422 Examiner aware of this information. The '422 patent originated from a different line of continuation applications than the '933 and '080 patents. (See also AM-ITC 00906488). 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...")). Thus, the examiner's notes in the file history of the '933 patent indicating that he reviewed the file from Interference 102,334, are irrelevant to the '422 prosecution and provide no indication whatsoever that the Baron-Goldwasser clinical study was disclosed during the prosecution of the '422 patent.

It is clear from the file history that led to the '868 patent that the Examiner could not have substantively considered any alleged submission of the Initial Determination of the ITC during prosecution until years after it was purportedly submitted. Prosecution of the application for the '868 patent was suspended in 1988 ('179 File History, Paper 16, 12/9/88 Letter) and 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 19, 5/1/89 Request for Withdrawal of Suspension;'179 File History, Paper 21, 5/6/89 Letter; Paper 22, Interference Digest; Paper 27, 2/2/93 Notice of Change of Address). The application leading to the '422 patent was filed on November 6, 1990 and according to legible portion of the Search Notes in the prosecution history of the '422 patent by December 1992, the examiner only "consulted claims in App. No. 07/113,179". (*See, e.g.*, Search Notes at AM-ITC 00899764).

Only specific portions of the Initial Determination of the ITC were submitted to the Interference Board and Amgen designated only specific portions of the opinion for the limited purpose of "identification", "patentability of the invention", "priority position" and "background information." Amgen did not designate for any purpose any discussion of the Baron-Goldwasser

clinical study. (*See* AM-ITC 00900641-AM-ITC 00900643). Similarly, Amgen referred the examiner only to pages 49-54 in submitting the opinion during the '933 prosecution. (AM-ITC00900550 - AM-ITC 00900555) and 153-160 (AM-ITC 00900629 - AM-ITC 00900636) of the decision. (*See* AM-ITC 00900641-AM-ITC 00900643). The referenced pages do not disclose the erythropoietin and HSA composition used or the results of the clinical study. 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).

Given the work load and the limited time that an examiner has to examine individual applications, it is highly unlikely that any of the examiners read the entirety of the opinion. However, reading the entirety of the opinion would provide no information beyond the misleading assertions regarding insufficient amounts of EPO, which incorrectly implied that no clinical study occured when in fact, Drs. Goldwasser and Baron had carried out a clinical study that would have been highly material to patentability. (AM-ITC 00900552-553).

**Failure to Disclose Dr. Strickland's HSA Contribution or Amgen's View that Regarding Obviousness of Such Compositions**

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, the '933 patent or the '080 patent, which all have claims to pharmaceutical compositions that would cover erythropoietin and HSA.

**Omissions and Misrepresentations Regarding Human EPO Fragments**

The common specification for the patents-in-suit sets forth information regarding human EPO fragment amino acid sequencing. (*See, e.g.*, '868 patent, col. 16:7-17:25 (example 1)). During the prosecution of the '422 patent, Applicant introduced new claims 64 and 65 (directed to a pharmaceutical composition and pharmaceutical preparation, respectively). Applicant argued for the patentability of these claims, noting that claim 64 is supported by Example 1 of the specification, which "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." (AM-ITC 00899473). Applicant further stated that in light of Examples 7 and 10 -- which disclosed production of human erythropoietin in COS-1 and CHO cells, respectively -- "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." AM-ITC 00899474. These claims were subsequently found allowable by Examiner Martinell. AM-ITC 00899723-25.

By pointing to Example 1 of the common specification as supporting file claim 64, Applicant affirmatively represented to the Examiner that the "invention" disclosed in claim 64 was fully supported by the original specification. Without such support, claim 64 would have been rejected for the addition of new matter.

Table I of the common specification, which is referenced in Example 1, lists the amino acid sequence of fragment T28 as "E-A-I-S-P-P-D-A-A-M-A-A-P-L-R." (AM-ITC 00898928; '868 patent, col. 16, l. 33). However, Applicant determined no later than 1985 that the amino acid sequence of T28 listed in Table 1 was incorrect, and should instead read "E-A-I-S-P-P-D-A-A-S-A-A-P-L-R." (*See, e.g.*, (Figure 4B-7 at AM-ITC 00596041-42; AM-ITC 00595293 ("The

complete amino acid sequence for human urinary-derived EPO protein in [sic] shown in Figure 4B-7")).

Furthermore, a scientific article published by Amgen scientists and Eugene Goldwasser in 1986 suggest that T28 sequence in described in the patent was incorrect. (Lai et al. 1986; Figure 1). This publication like the sequence given to the FDA indicates that T28 has a serine and not a methionine. This publication was received for publication on August 26, 1985 demonstrating that, Amgen was aware that the data in the patent regarding the sequence of tryptic fragment T28 was not correct by at least that time. The authors from Amgen and Dr. Goldwasser concluded that the amino acid in position 126 of erythropoietin isolated from human urine is serine, not methionine as suggested by the patent. Regarding this amino acid the authors state

> Sequence analysis peptides T28 and 2S63 indicated a serine at position 120 and no identifiable PTH for position 126. However, amino acid composition analysis revealed the presence of 2 serine residues in this fragment. Analysis if the DNA sequence indicated that a serine is present at position 126 (10, 11). One possible explanation for these results is that position 126 is a glycosylated serine.

Drafts of this publication indicate that Amgen originally believed that human urinary erythropoietin contained a methionine at position 126 (numbering provided in Figure 1 of Lai et al). (*See, e.g.*, AM-ITC 00072323 - 44; AM-ITC 00072302 - 27; AM-ITC 00072538 - 559; AM-ITC 00138725 - 55; AM-ITC 00145452 - 534; AM-ITC 00071306 - 331; AM-ITC 00071332 - 61; AM-ITC 00071642 - 56; AM-ITC 00071657 - 79; AM-ITC 00071995 - 2010; AM-ITC 00072060 - 96; AM-ITC 00072249 - 95).

A partial manuscript accompanying a letter to Por Lai from Eugene Goldwasser, dated October 9, 1984, contains no discussion of amino acid 126. (AM-ITC 00072274 - 83). What appears to be a early version of the manuscript, containing numerous hand-written comments, states

> Comparison of the sequence determined from the protein with that determined from the cloned gene shows only one difference, at residue 126; the DNA sequence indicates a serine at that position whereas the protein has a methionine. We do not yet know the reason for this difference but it may be related to the fact that the EPO used was prepared from urine collected in Japan while the genomic DNA was probably from the kidney of a Caucasian.

(AM-ITC 00072262). This same statement appears in another version of the manuscript. (*See, e.g.*, AM-ITC 00072302-22 at 11). Fig. 1 of this version of the manuscript shows the amino acid sequence of both "Cloned EPO" and Urinary EPO" where the amino acid residue at position 126 is shown as Ser in the former, and Met in the latter. (AM-ITC 000723315, AM-ITC 00072320 Thus, at this point in time the authors believed urinary EPO to have a methionine at position 126.

On March 8, 1985 Dr. Goldwasser informed Dr. Lai of Amgen about a publication from Genetics Institute which may have been Amgen's first indication that T28 was incorrect. In a letter to Por Lai, Dr. Goldwasser states:

> I think our paper should have this addition at the very end - just before "Acknowledgements."
>
> In the final stage of preparation of this paper, a report by Jacobs et al (13) appeared in which the primary structure of human erythropoietin, deduced in part from amino acid sequencing and in part from the DNA sequence, was revealed. Our sequence agrees completely with theirs, with the exception of the methionine at position 126. They find a serine by both amino acid sequencing and from the DNA sequence.

(AM-ITC 00211638). The statement proposed by Dr. Goldwasser appears in a version of the manuscript which accompanies a hand written draft of a letter from P. Lai to the editor of the Journal of Biological Chemistry. (AM-ITC-00071306 - 331 at 320).

Another manuscript states:

> Sequence analysis of peptides T28 and S38 indicated a methionine residue at position 126. However, amino acid composition analysis of S38 did not reveal any significant amount of methionine, instead two serine residues were found in this fragment. Analysis of the DNA sequence indicated that a serine is present at this position [citing reference 4] One possible explanation for these results is that position 126 is a modified serine such as sulfated or phosphorylated residue.

> Modification by carbohydrate moiety seems unlikely since EPO lacks N-acetylgalactosamine [citing reference 6]. ...

(AM-ITC 00072538 - 559 at 547).

Similarly, the document entitled "Supplemental Material to Structural Characterization of Human Erythropoietin" contains a figure showing only the sequence of urinary EPO and has a serine at position 126:

> All of the residues were assigned positions by sequencing and positive identification except the asparagines at positions 24, 38, and 83 and one serine at position 126 which was identified and assigned by composition analysis of peptide T28 (data not shown)."

(AM-ITC 00138725-755 at 729).

Another version of the manuscript accompanies a letterdated July 31, 1985 from Eugene Goldwasser to Por Lai. The letter states "Finally here is the figure for the paper. I hope we can get it out without too much more delay." The manuscript, which contains hand-written annotations, states:

> Sequence analysis of peptides T28 and 2S63 indicated a serine at position 120 and no identifiable PTH for position 126. However, amino acid composition analysis revealed the presence of 2 serine residues in this fragment. Analysis of the DNA sequence indicated that a serine is present at position 126 (10, 11). One possible explanation for these results is that position 126 is a glycosylated serine. In fact, our preliminary results indicated that galactosamine whose precursor, N-acetylgalactosamine is the linking sugar at hydroxy amino acids was detected in the composition analysis of peptides T28 and 2S63 (data not shown).

(AM-ITC 00071995-2010 at 2002).

Despite the numerous documents that show those involved with Applicant and the patents-in-suit knew that the sequence was wrong, Applicant never disclosed this error to the Examiner. Had Applicant disclosed the error, this would have resulted in a rejection for the addition of new matter. Even if the recited sequence was a typographical error, a subsequent correction would nonetheless be the addition of new matter unless it was an obvious error. It is

clear, however, that the error was not obvious. The common specification states that erythropoietin is "a substance for which no substantial amino acid sequence information has been published." ('868 patent, col. 9, ll. 4-7). Therefore, without that information, nothing about the particular amino acid sequence could have been obvious. In any event, additional documents confirm that the recited sequence for T28 was not an error. (*See, e.g.*, AM-ITC 00415129). Even if, for argument's sake, Applicant knew of two different forms of human urinary EPO, one with an "M" and one with a glycosylated "S" -- and, thus, there was not a true "error" to disclose -- it would nonetheless have been important to disclose this information to the Examiner, especially in light of Applicant's argument that its claimed invention differed in glycosylation from human urinary EPO. Applicant would have then been obligated to show a difference in glycosylation as compared to two different forms of urinary EPO.

By failing to disclose material information regarding the amino acid sequence of T28, Applicant mislead the Examiner as to the existence of proper support in the specification for the claimed invention. As a direct result, Amgen obtained a patent to claims which likely introduced new matter. Had Applicant disclosed this information, the claims would have been rejected for adding new matter under 35 U.S.C. §112, ¶1. Accordingly, the '422 patent is unenforceable for inequitable conduct.

**Additional Misrepresentations Regarding Sulfate Content of EPO**

In his 1988 Declaration submitted to support Amgen's arguments regarding differences between u-EPO and r-HuEPO Dr. Strickland concludes from his experiments that "u-EPO contains sialidase resistant negative charges not found in r-HuEPO". (*See* AM-ITC 00941134). Dr. Strickland cites to a paper by Takeuchi et al. However, nowhere does Dr. Strickland disclose that 1) he was in contact with Dr. Takeuchi at a time prior to signing his 1988 Declaration or that

Dr. Takeuchi had provided him with information contradictory to Dr. Stricklands conclusion regarding differences based on sialidase resistant negative charges. (3/9/2007 Strickland Depo. Tr. 299:7 - 300:14). Specifically, Dr. Strickland was aware of information from Dr. Takeuchi that the "differences" that Dr. Strickland reported to the PTO were potentially due to simply the use of old enzyme in the experiments performed by Dr. Strickland. (3/9/2007 Strickland Depo. Tr. 305:14 - 309:10; AM-ITC 00067214 - 259 at 241). This alternative explanation would have been important to a reasonable examiner in considering patentability. In that Dr. Strickland was is in possession of information that potentially contradicted a position taken in his declaration, he was under an obligation to disclose that information.

**Failure to Disclose Information Regarding CHO Cells**

Amgen has asserted that the use of chinese hamster ovary ("CHO")cells to express erythropoietin was routine and did not involve any inventive contribution. If Amgen changes its position and asserts that the use of CHO cells was inventive, then Amgen's attorneys and Dr. Lin affirmatively withheld highly material information relating to individuals who contributed to the invention of the patents-in-suit. Dr. Lin has admitted that at the time of the invention individuals at the American Type Culture Collection ("ATCC") contributed the idea to use CHO cells.

> Q. That's fine. And who suggested using CHO cells for the expression of the EPO gene?
>
> A. I may have suggested -- besides actually CHO cells, I also have actually look into other cells. I think there's another cell. I talk to the people at ATCC at the time. There's only two stable cells that can be used -- I mean the stable cell line they could use. One is the other cells. Now I cannot remember. There's another cell. It's also very stable for the purpose of production. So CHO cells and the other one, yes, which I -- I talked to one of the guys at ATCC.

(3/28/07 Lin Tr. at 63).

> Q. So your testimony is that you picked CHO cells because you called the ATCC, and they told you that's what you should use?

[objection]

THE WITNESS: No, no, no. I not call the ATCC. I was looking for cells of which would be suitable for commercial production. Therefore, the cells -- cell line to be used had to be stable so that's why I would -- try to decide which cell line is to be used. So I call my friend at ATCC and talked to people to see what the -- what the cell line would be good to use. And the CHO cell come up as one. And the other one, I just cannot remember. There's another one that is also very stable.

BY MS. BEN-AMI:

Q. Who is your friend at the ATCC?

A. At the time, I have a friend who's a curator at ATCC. Dr. Tsong, I believe -- Dr. Tsong.

Q. Can you spell that?

A. Let me think if I can remember the name. Sung Chang Tsong. It's Chinese. He's senior to me. He's the curator at ATCC.

Q. Can you try to spell that for us? I know you could be wrong, but if you could try. Do you want to write it down?

A. I would spell it probably, S-u-n-g, Sung; Chang, would be, C-h-a-n-g. Something like that; Tsong, would be, like -- Tsong would be T-s-o-n-g. That would be the last name. And I think he may have refer me to the other guy. The other guy -- what's his name? I think it's Dr. Cheng -- Dr. Cheng, C-h-e-n-g. Yeah, he -- at the time, I believe he was working in the mammalian cell group over there.

Q. At the ATCC?

A. Yes. One of the --

Q. So you asked them what cell lines would be very stable?

A. That's right, for culture purpose, yeah. Because my concern is for mammalian production, the cell line had to be stable. So I talked to --

Q. And they suggested two cell lines to you?

A. Definitely one of the cell line was suggested. Yeah.

The other one -- he say that the other cell line may be just as stable or may be even better than CHO cell. That's what he tell me, as I recall.

Q. But he suggested CHO cell and one other cell line?

A. Yes. He suggest -- I don't know he suggest CHO cell. He basically tell me which cells are stable. It does not mean he suggested -- he did say these other cells are stable.

Q. Which cells?

A. The CHO and the other one. I forgot what's the other one.

Q. Okay.

A. Yeah, I forgot the name of the cell now.

Q. Okay.

A. But if you talk to ATCC people, they probably also still remember what cell line --they probably have information about -- what information what cell lines are stable in the culture.

(Id. at 64-67.)

Amgen was indisputably aware that information regarding those responsible for inventive contributions to any claim of the patents-in-suit would have been material to prosecution of its patents. With each application filed, Dr. Lin submitted a sworn declaration stating that he was the sole inventor of claimed subject matter. (*See* SN 06/675,298 "Declaration for Patent Application, signed 11/29/84; '179 File History (*e.g.* AM-ITC 00953127); '381 File History (*e.g.* AM-ITC 00898283); '741 File History (*e.g.* AM-ITC 00899006); '556 File History (*e.g.* AM-ITC 00868031); '369 File History (*e.g.* AM-ITC 00898596)). At no time did Dr. Lin or Amgen disclose any contribution made by Drs. Tsong or Dr. Cheng at the ATCC. A protest under 37 C.F.R. § 1.291(a) was filed on July 23, 1993 during the prosecution of the 07/119,178 application, which resulted in the '868 patent. In that protest, Dr. Por Lai asserted that he made a critical contribution to the invention claimed. Included in the claims at issue were claims drawn to the production of erythropoietin in CHO cells. ('179 file history, Paper 8, 6/1/88 Second

Preliminary Amendment at 4). At no time during the course of the PTO's consideration of that protest did Amgen or Dr. Lin disclose the contribution by anybody other than Dr. Lin.

**Failure to Disclose Prior Art Relating to "PEG-EPO"**

Amgen's expert, Dr. Katre asserts that U.S. Patent No. 4,179,337 ("the '337 patent") by Davis et al., which issued in 1979, discloses pegylated erythropoietin compounds or "peg-EPO". It is Amgen's position that the claims of the patents-in-suit cover "Peg-EPO." Roche does not agree with Amgen's improper characterization of Roche's CERA product or the assertions by Amgen and Dr. Katre. However, based on Amgen's assertions the '337 patent would have been highly material prior art, which Amgen failed to disclose during prosecution of the patents-in-suit. As Dr. Lin recently testified at this deposition, he was aware of pegylation at the time that the patents-in-suit were filed. Dr. Lin testified as follows:

> Q. By 1984, had you heard of the process of pegylation?
>
> A. Yeah, pegylation technology exists at that time -- even before this time, yes. I remember that. There are product which has been pegylated, actually had been used in human.

(3/28/07 Lin Tr. at 90).

Amgen and Dr. Lin were undoubtedly aware of the '337 patent, which is highly relevant prior art to the claims of the patents-in-suit, if those claims are construed as Amgen contends. Thus, Amgen's failure to disclose the '337 patent constitutes yet another failure by Amgen to disclose material information that Amgen knew about and should have disclosed.

**Additional Evidence of Intent**

The file histories of the patent-in-suit evidence an intentional pattern to deceive the U.S. Patent Office to secure additional patent and claims to extend its monopoly beyond the original '008 patent which expired on October 27, 2004. For example, Amgen secured the '349, '933, '080 and '422 patent claims to protect a product that was already in nature (35 U.S.C. §101) and

now asserts that its product claims are not limited by their method of manufacture. (*See, e.g.*, AM-ITC 00906512). By violating the duty of candor and disclosure as set forth in Roche's responses to Amgen's Interrogatory No. 26 and the expert reports incorporated by reference, Amgen has successfully secured dozens of additional patent claims, extending its monopoly against potential competition and, in turn, unfairly shielding its billions of dollars in annual sales (and will continue to do so through 2015).

Plainly, sales in the United States have been lucrative for Amgen, and Amgen expects a continuing increase in patient demand for its products. (*See, e.g.*, 1/25/07 Amgen Press Release at http://www.amgen.com/media/media_pr_detail.jsp?year=2007&releaseID=954402 ("Underlying demand in free-standing dialysis clinics remained consistent with an annual patient population growth of 3-4 percent")). Given the annual revenue generated by Epogen® after its approval by the U.S. Food and Drug Administration in 1989, Amgen had every reason to secure additional patent claims. Since approval for Epogen®, Amgen has reported sales of approximately $25,186,300,000 in the United States. (Amgen Inc., 10K Filings 1991-2006; see also AM 44 1508568). Even, after the expiration of the '008 patent, Amgen reported another approximately $2,455,000,000 in U.S. sales for 2005 and $2,511,000,000 in U.S. sales for 2006. Similarly, its Aranesp® product -- which Amgen asserts is covered by the '698 patent-in-suit -- has generated over approximately $7,718,600,000 in sales since 2001 with approximately $4,894,000,000 of the total amount due to sales since the '008 patent expired (Amgen Inc., 10K Filings 1991-2006).

Accordingly, Amgen has kept its monopoly alive by filing numerous continuation applications over many years in an attempt to add claims to prevent competitors from entering the U.S. with products. But for Amgen's misconduct there (1) would be no patent claims

currently in force, including Amgen's numerous product claims and its process claims (that should have at a minimum been disclaimed over the expired '008 patent to gain allowance) and (2) competitive products would be available. Given the commercial environment and Amgen's sales figures, it had every reason to secure its additional claims and patents by whatever means deemed necessary.

DATED: May 1, 2007

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By its attorneys,

/s/ Patricia A. Carson

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CONTAINS CONFIDENTIAL MATERIAL
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CERTIFICATE OF SERVICE

I hereby certify that a copy of DEFENDANTS' SECOND SUPPLEMENTAL RESPONSES AND OBJECTIONS TO AMGEN INC.'S THIRD SET OF INTERROGATORIES TO DEFENDANTS (NO. 26) was served upon an attorney of record for the plaintiff at the listed law firm by email.

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