EXHIBIT 1
Part 1 of 3

CONTAINS CONFIDENTIAL MATERIAL
PURSUANT 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

DEFENDANTS' SECOND SUPPLEMENTAL RESPONSES AND OBJECTIONS TO AMGEN INC.'S THIRD SET OF INTERROGATORIES TO DEFENDANTS (NO. 26)

Defendants and Counterclaim-plaintiffs F. Hoffmann-La Roche Ltd., Roche Diagnostics GmbH, and Hoffmann-La Roche Inc. (collectively "Roche") hereby object and respond to Plaintiff and Counterclaim-defendant Amgen Inc.'s ("Amgen") Third Set of Interrogatories (No. 26).

GENERAL OBJECTIONS

The following general objections apply to all of Roche's responses and shall be incorporated in each response as if fully set forth therein ("General Objections"). To the extent specific General Objections are cited in response to a specific interrogatory, those specific General Objections are provided because they are believed to be particularly applicable to the specific interrogatory and are not to be construed as waiver of any other General Objections applicable to the interrogatory.

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1. Roche hereby incorporates all objections to definitions and instructions as set forth in Defendants' Responses and Objections to Plaintiff Amgen Inc.'s Third Set of Interrogatories (No. 26), dated March 14, 2007 and Defendants' Supplemental Responses and Objections to Plaintiff Amgen Inc.'s Third Set of Interrogatories (No. 26), dated April 2, 2007.

2. In all instances Roche intends to preserve its claim of attorney-client privilege and/or work product immunity in responding to Amgen's Interrogatories. If any such information is disclosed, except pursuant to a specific written agreement covering such information, the disclosure is inadvertent and shall not be construed as an intention to waive any applicable privilege. Roche will identify information excluded from discovery on grounds of attorney-client privilege and/or work product immunity and will expressly identify the basis for the privilege or immunity asserted in manner consistent with the Federal Rules of Civil Procedure. Roche also reserves the right to assert other privileges under Fed. R. Evid. 501.

3. Moreover, Roche specifically reserves its right to supplement its responses to interrogatories that deal with the obviousness as it relates to the standard of materiality. As Amgen is aware, the Supreme Court just yesterday issued its opinion in *KSR International Co. v. Teleflex Inc.*, 550 U.S. __ (2007), where the Court eliminated the requirement of a specific "teaching, suggestion, or motivation" within the prior art for purposes of finding obviousness under 35 U.S.C. § 103. Roche is still studying the ramifications of this decision. In addition, the Supreme Court's decision opined on other issues which may also affect the materiality standard. Roche will timely supplement its responses as soon as it has fully investigated this decision and its impact on this case.

4. Moreover, Amgen is still producing documents and supplemental expert reports, and as a result, Roche reserves its right to supplement these discovery responses in view of

Amgen's continued production. Moreover, Amgen has had Roche's Expert Reports On Invalidity and Unenforceability since April 6, 2007, but has not made any effort to supplement its interrogatory responses regarding these issues. Therefore, Roche reserves its right to supplement these discovery responses to contend with Amgen's responses.

INTERROGATORIES

In addition to all prior responses and subject to and without waiver of Roche's previously propounded Specific Objections and General Objections set forth above all of which are incorporated herein by reference, Defendants respond as follows.

INTERROGATORY NO. 26

For each patent-in-suit that you contend is unenforceable due to inequitable conduct (including the allegations set forth in paragraphs 33-88 of Roche's [Proposed] First Amended Answer, dated December 8, 2006): separately and specifically describe all legal, factual, and evidentiary bases for each allegation of a material omission or misrepresentation and corresponding intent to deceive the patent office, including identifying the specific documents, statements therein, witnesses, testimony, and things which support, refute, or otherwise relate to each such contention (*e.g.*, provide all the requested information for your allegations that "Amgen failed to disclose ***arguments*** it made during opposition proceedings in Europe involving Genetics Institute's EP 411, 678 ('678 patent) and EP 209 539 ('539 patent) . . . ." (Roche's [Proposed] First Amended Answer ¶ 49) (emphasis added), "Amgen also failed to disclose ***inconsistent arguments*** made during the following proceedings in Europe . . . ." (¶ 49, n. 1) (emphasis added), "[Amgen failed] to disclose ***arguments*** that were raised during the opposition proceedings to its Kirin-Amgen European Patent Application No. 0 148 605 . . . ." (¶ 49) (emphasis added), "Amgen's ***understanding***, (and ***admissions*** to the Patent Office) that the claimed product described by the pending '178 claims was merely the inherent product of the process . . . ." (¶ 53) (emphasis added), "[Amgen] relied on **statements and information** regarding the molecular weights and carbohydrate compositions of r-EPO and u-EPO that were inconsistent, and refuted ***the positions Amgen took*** during prosecution of its patents before the PTO, and in the *Fritsch et al. v. Lin* patent interference No. 102, 334." (¶ 76) (emphasis added), "***Additional internal documents*** from Dr. Egrie provide evidence regarding glycosylation inconsistent with ***the positions Amgen took*** during the prosecution of the patents." (¶ 87) (emphasis added), and "Amgen made ***statements to the FDA*** that directly contradict ***the positions Amgen took*** in arguing patentability of its EPO claims to the PTO." (¶ 88) (emphasis added); identify each person, other than counsel, who furnished information for or was consulted regarding your response to this Interrogatory, stating the nature and substance of each such person's knowledge or information; and identify the three individuals affiliated with Roche, other than counsel, most knowledgeable regarding the subject matter of this Interrogatory, stating the nature and substance of each such person's knowledge or information.

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SUPPLEMENTAL RESPONSE TO INTERROGATORY NO. 26:

Roche objects to Interrogatory No. 16 to the extent that it is premature because fact discovery is ongoing, seeks expert information pursuant to Fed. R. Civ. P. 26(b)(4)(A), seeks information subject to the attorney-client privilege and/or attorney work-product doctrine and is a premature contention interrogatory. Without waiving these objections, Roche respond that:

Throughout the prosecution of the patents-in-suit (including relevant priority applications), Amgen made numerous material misrepresentations to the examiners of the United States Patent and Trademark Office ("PTO") and omitted material information to purposefully prosecute otherwise unpatentable claims to secure its monopoly power beyond the statutory term. Amgen's pattern of conduct includes:

- affirmative and explicit misrepresentations regarding the state of the prior art;
- affirmative and explicit misrepresentations and omissions regarding the differences (or lack thereof) between Lin's claimed "inventions" and the prior art;
- burying prior art references and material information so that the examiner would be likely to ignore such information; and
- directing examiners away from substantively considering material information that a reasonable examiner would consider important.

This misconduct evidences a consistent and intentional scheme by Amgen to intentionally deceive and mislead the PTO into issuing its claims. More specifically:

Amgen's Omissions to Secure Claims to Extend Its Monopoly

The patents-in-suit are unenforceable because individuals including, but not limited to Amgen's patent attorneys -- Michael Borun, Steven Odre and Stuart Watt -- associated with the filing and prosecution of these patents and acting as agents and/or with the knowledge of

plaintiff Amgen, misrepresented material facts with the intent to deceive the PTO for purposes of overcoming a double patenting rejection based on Amgen's earlier filed and issued '008 patent. By way of these misrepresentations Amgen purposefully secured from the PTO unpatentable claims that extended its monopoly power beyond the statutory term for its invention. (AM-ITC 00873512-13 (process claims 69-72 in Ser. No. 675,258); AM-ITC 00873533-41 and AM-ITC 00873605-611(rejecting process claims); AM-ITC 00873616-43 (canceling process claims)).

During Amgen's prosecution of Ser. No. 113,179 (the "'179 application"), which issued as the '868 patent, Amgen faced a double patenting rejection of all its pending claims (70 and 72-75) on grounds that these process claims were not patentably distinct from claims 1-6 of the '008 patent because it would have been obvious to one of skill to use the claimed erythropoietin encoding DNA of the '008 patent in prior art methods for host cell expression. (*e.g.* AM-ITC 00953685 (The pending claims "are not patentably distinct from each other because it would have been obvious to one of ordinary skill in the art to modify the method of Yokota et al. by substituting the instant erythropoietin encoding DNA [of the '008 patent] for the DNA encoding GM-CSF.").

Amgen overcame that rejection only by (1) misleading the examiner into believing that a dispositive judicial determination had already confirmed that none of the '008 patent claims encompassed subject matter of its pending '179 application process claims, (2) misleading the examiner into believing that the Patent Office in interference proceedings had already determined the subject matter of its pending '179 application process claims to be patentably distinct from any of the '008 claims, and (3) by failing to disclose arguments it made before the Patent Office Board of Patent Appeals and Interferences (the "Board"), as well as in opposition proceedings in Europe involving Genetics Institute's EP 411 678 (the '678 patent) and EP 209

539 (the '539 patent), inconsistent with and refuting its arguments for patentability of its pending '179 application process claims.

In particular, during the '179 prosecution, Mr. Borun misrepresented the court's decision in *Amgen, Inc. v. U.S. Int'l Trade Comm'n*, 902 F.2d 1532 (Fed. Cir. 1990), stating: "There has thus been a judicial determination that rights in the subject matter of '008 patent claims do not extend to the subject matter of the process claims herein . . . ." (AM-ITC 00953697). The Federal Circuit, however, considered only whether the composition claims fell within the ambit of 19 USC § 1337(g), which provides patentees the right to bring actions against foreign companies that allegedly infringe a patented process abroad. 902 F.2d at 1537. Significantly, the Court did not address whether the product claims were patentably distinct from the process Amgen was attempting to claim in the '179 application. Although Amgen argued "Chugai was importing rEPO and that the rEPO was made by a process covered by the '008 patent." (902 F.2d 1536), the Court held only that the claims of the '008 patent could not be used in Section 1337(g) actions because they were not directed to a process. Indeed, Amgen had voluntarily canceled the process claims pending in the application that led to the '008 patent after receiving multiple prior at rejection to avoid substantive arguments regarding patentability of the claims. (AM-ITC 00873642).

Similarly, Amgen argued against double patenting citing to a decision before the European Patent Office Board of Appeals in Amgen's corresponding European Patent 0 148 605 as "factual support for patentable distinctiveness of the process claims". (AM-ITC 00953698-99). However, the European Board never actually addressed whether the process claims were patentable in light of Amgen's own '008 patent claims. Therefore, neither the ITC decision or

the European Board held the process claims were patentable over the '008 patent as Amgen misrepresented to the examiner.

Additionally, during the '179 prosecution, Amgen misrepresented to Examiner Martinell that in connection with Interference No. 102,096 (the "Fritsch I interference") (with its sole count identical to claim 2 of the '008 patent) and Interference No. 102,097 (the "Fritsch II interference") (with its sole count identical to then pending '179 application claim 65) "it has thus been the position of the Patent and Trademark Office that the production process subject matter claimed herein was patentably distinct from the DNA-related subject matter claimed in U.S. 4,703,008." (AM-ITC 00953697).

Not only did this misrepresent the position of the Board, which made no such conclusion, Amgen failed to inform the examiner that in the Fritsch II interference it took the entirely contradictory position that its process claims were inherently part and parcel of the same invention as claimed in its '008 patent.

> While the count is directed to a process for preparing *in vivo* biologically active EPO using a mammalian host cell transfected or transformed with an isolated DNA sequence encoding human EPO [i.e., the process patent claims], and the litigation was directed to the purified and isolated DNA sequence and host cells transfected or transformed thereby [i.e., the '008 DNA claims], ***it is evident that these are only different manifestations of the same invention*** as acknowledged by Fritsch et al in their Motion Q here (and in Motion G in Interference No. 102,096). Clearly, the whole purpose and intent of the purified and isolated DNA sequence encoding human EPO (and host cells transfected therewith) at issue in the litigation was to express *in vivo* biologically active human EPO. Stated otherwise, the process language of the Lin patent claims at issue in the litigation ("encoding human EPO") [see '008 patent claims] is, for all intents and purposes, a description of the present count.

(AM-ITC 00337677-78 (emphasis added)).

Significantly, not only did Mr. Borun submit Applicant's October 7, 1994 Amendment and Remarks in the '179 prosecution (AM-ITC 00953701), Mr. Borun, and Amgen in-house counsel, Mr. Odre, appear as "of counsel" on the Lin Brief, evidencing his obvious familiarity

with these contradictory positions that Amgen relied on during the interference and his knowing and intentional misrepresentation of those positions in prosecuting the '179 application.

Tellingly, Amgen also failed to inform the examiner that in the Fritsch II interference, it had argued that resolving priority issues in regard to the count for the DNA sequence in the Fritsch I interference would necessarily determine those issues in regard to its process claims:

> The same is true with regard to the count of Interference 102,097 [process for making EPO], ***if Lin was the first to invent a host cell containing a DNA sequence in a manner allowing the host cell to express rEPO as determined by the Court [DNA count], he is of necessity the first to invent the process of making rEPO using such the host cell*** (see the count of Interference 102,097) [process for making EPO]."

(AM-ITC 00328343 (emphasis in original)).

> "Fritsch [Genetics Institute] errs in saying that the District Court case did not involve the count (process for making EPO) of Interference No. 102,097. ***The Court assessed the priority evidence regarding the DNA sequence used to make EPO and the reduction to practice of the sequence necessarily and inherently includes the use of that sequence to make EPO according to the count of Interference No. 102,097.***"

(AM-ITC 00328349 (emphasis in original)).

Moreover, Amgen failed to disclose arguments it made during opposition proceedings in Europe involving Genetics Institute's EP 411 678 ('678 patent) and EP 209 539 ('539 patent) that were similarly inconsistent with and refuted its arguments for the patentability of its '179 application process claims. In this regard, Amgen acknowledged that its process and resulting *in vivo* biologically active erythropoietin was merely an obvious and inherent result of expressing the DNA sequence encoding human erythropoietin in a host cell: "the particular type of glycosylation linkages was simply a result of the type of host cell used to produce the recombinant erythropoietin." (EP 411

678 Opposition Proceedings, Statement of Grounds submitted by Amgen 10/8/1992).* Amgen's consistent pattern of failing to apprise the United States examiners of material information from European proceedings is similarly shown through its failure to disclose arguments that were raised during the opposition proceedings to its Kirin-Amgen European Patent Application No. 0 148 605 regarding the high materiality of errors in the data corresponding to Example 10 of its US patent application. (European Tech. Board of Appeals 11/21/1994 ("[A]s admitted by the Respondents, the carbohydrate analysis performed in Example 10 was erroneous."); *see also* 9/6/2000 Borun Trial Tr. 2854:9-25 (incorrect hexose/fucose values in U.S. Patents)).

Amgen also asserted that it was inappropriate for the examiner to consider prior art (the Yokota 4,695,542 patent) in conjunction with the claims of the '008 patent to show that the pending claims were obvious arguing that "as noted in the decisional authorities, [double patenting] must be determined through consideration of the *claims* of the pending application and issued patent -- and not with reference to the prior art." (AM-ITC 00953700). Amgen presented no authority in support of this proposition, and consequently misstated the law, which provides that consideration of prior art may be necessary to determine whether one of skill in the art would deem the later claim to be merely an obvious variation on the earlier one. *See e.g.* MPEP §804 ("Claim [1] rejected

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* In addition, Amgen also failed to disclose inconsistent arguments made during the following proceedings in Europe: (1) Ortho Pharmaceutical Corp. v. Boehringer Mannheim GmbH (Landgericht Dusseldorf (4 O 150/91)) (Patent infringement action for E 0 148 605), (2) Boehringer Mannheim GmbH v. Janssen-Cilag GmbH (4 O 229/91, Landgericht Dusseldorf) (Cilag I), EP 0 205 564 (3) Boehringer Mannheim GmbH v. Janssen-Cilag GmbH (4 O 58/92, Landgericht Dusseldorf) (Cilag II), EP 0 411 678; (4) Boehringer Mannheim GmbH v Kirin-Amgen, (3 Ni 32/93, Bundespatentgericht (BPG)) and appeals therefrom and (5) Kirin-Amgen and Ortho Pharmaceuticals v. Boehringer Mannheim GmbH and Boehringer Mannheim UK Ltd., The High Court Of Justice Chancery Division, Patents Court (CH 1993-K-No. 937).

on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim [2] of U.S. Patent No. [3] in view of [4], [5].").*

Similarly, with respect to a double patenting rejection over Lai U.S. 4,667,016, Amgen argued that *In re Braat*, 937 F.2d 589 (Fed. Cir. 1991) required the use of a two-way non-obviousness test to determine double patenting. (AM-ITC 00953643-47). Subsequently, in arguing against double-patenting over the '008 claims, Amgen again cited to *Braat* in arguing that the double-patenting rejection was improper, but did not explain that the two-way non-obviousness test was not applicable to the rejection over the '008 patent. (AM-ITC 00953694-96).

Throughout its response to the PTO's rejection for double patenting, Amgen therefore intentionally misrepresented its own understanding of the claims, misrepresented the facts of prior proceedings and misstated legal standards. This fraud on the PTO was motivated by Amgen's need to improperly extend the life of its EPO invention by maintaining and prosecuting applications that issued into patents, which were obvious over an earlier issued and now expired patent. In response to this conduct, Examiner Martinell allowed all of the pending claims, plainly demonstrating his reliance on Amgen's misrepresentations. (AM-ITC 00953708). But for these misrepresentations, the examiner would not have allowed the '179 claims to issue, as they did in the '868 patent, in any patent entitled to a term exceeding that of the earlier commonly owned '008 patent.

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* Furthermore, as discussed below, Mr. Borun also argued that the obviousness-type double patenting rejection based in part on Yokota *et al.* was improper and irrelevant "because human M-CSF is not a obligate human glycoprotein." (AM-ITC 00953700).

Amgen's misrepresentations during prosecution of the '179 application (which issued as the '868 patent) relating to the patentability of its pending product claims over the '008 patent are also material to the product claims of the other later issued patents in the '179 family -- i.e., the '698, '422 and '349 patents. But for such misrepresentations, Examiner Martinell would not have allowed the claims of these patents to issue, as they did, in patents having a term exceeding that of Amgen's earlier commonly owned '008 patent.

Moreover, Amgen's understanding, (and admissions to the Patent Office) that the claimed product described by the pending '178 claims was merely the inherent product of the process Amgen was attempting to claim in the '179 prosecution renders these misrepresentations just as material to Amgen's prosecution of process claims in the '178 line of applications, which ultimately issued as the '080 and '933 patents, as they were to the claims of the '868 patent.

- AM-ITC 00941168: "All product claims are now product-by-process claims."
- AM-ITC 00941216:

> Applicant has added new claims 76-83, which are similar to cancelled claims 67-75, but which specify that the DNA sequences encode human erythropoietin. These new claims parallel claim 2 of U.S. Patent No. 4,703,008 (Lin '008 patent), the parent of the instant application.

- AM-ITC 00941217 (emphasis in original):

> The [Amgen v. Chugai Federal Circuit] decision is thought to be fully dispositive of not only the priority of invention issues in both interferences, and any priority issue in the subject application. Therefore, it is submitted that 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 00868086: "Applicant notes from the outset that this claimed subject matter has its origins in great-grandparent application U.S. Serial No. 06/675,298 [the '008 patent]."

But for such misrepresentations, Examiner Martinell would not have allowed the claims of these patents to issue, as they did, in patents having a term exceeding that of Amgen's earlier commonly owned '008 patent. Accordingly, at least the '868, '698, '422 and '349 patents are unenforceable for inequitable conduct.

To the extent that Amgen and its attorneys now argue that statements submitted to the PTO during the *Fritsch v. Lin* interferences are not admissions by Amgen and its counsel that the various asserted claims are manifestations of the same invention (e.g. 3/2/07 Borun Depo. Tr. 160-164, 173-178, 180-187, 190-191, 194-202, 271-274) and include limitations that would have been routine to one of skill in the art, then the whole predicate on which Amgen succeeded over Fritsch in the interference to claim priority is wrong. The PTO made plain that it relied upon arguments by Lin that an inventor need not "be personally involved in carrying out process steps" "where implementation does not require the exercise of inventive skill", such as expression of the EPO gene in mammalian host cells and isolation of the resulting glycoprotein. *Fritsch v. Lin*, 21 USPQ2d 1737, 1739 (Bd. Pat. App & Interf. 1992). The Board held that "We agree with Lin", there is "no evidence that the work done at Amgen relating to the expression of the EPO gene in mammalian host cells and isolation of the resulting glycoprotein product involved anything other than the exercise of ordinary skill by practitioners in that field." *Id.* Accordingly, if not binding admissions, then Amgen committed inequitable conduct during the interferences to secure Lin's claims, each of the patents-in-suit is tainted by that conduct and, consequently, each patent-in-suit is unenforceable.

Amgen's Misconduct to Overcome the Lai Double-Patenting Rejection

During prosecution of Ser. No. 113,179 ("the '179 application"), Examiner Hodges issued a double patenting rejection over Lai U.S. 4,667,016 ("the Lai '016 patent") (AM-ITC00953591-601). The Lai '016 patent issued on May 19, 1987 from Ser. No. 06/747,119, filed June 20, 1985 and expressly incorporated by reference Ser. No. 675,298, PCT No. US84/02021 and WO85/02610. (Lai '016 patent, 2:64-3:6; see also col. 4:33-38). The '179 application was filed October 23, 1987 and is a continuation of Ser. No. 675,298 filed November 30, 1984, which in-turn is a CIP of three prior applications filed December 13, 1983, February 21, 1984, and September 28, 1984.

In response to the double patenting rejection, as explained above, Amgen and Mr. Borun stated the two-way test for double patenting applies because the rejected claims of the '179 purportedly are entitled to an effective filing date earlier than the filing date of the Lai '016 patent. (AM-ITC 00953647 ("Applicant has thus demonstrated two-way *non-obviousness* concerning the subject matter of the present claims and claim 9 of the Lai *et al.* patent.", "Applicant's above noted demonstrations of two-way non-obviousness and lack of any timewise 'extension' of patent protection are believed to establish that no proper basis exists for application of the judicially-created doctrine of double-patenting."; see also AM-ITC 00953603 (Examiner Interview including Messrs. Borun, Odre and Watt)). He also blatantly claimed that "issuance of the pending claims in the present ['179] application would provide no extension whenever the protection of the Lai *et al.*, much less an unjustified extension thereof." (AM-ITC 00953645).

Examiner Hodges relied on the applicant's representations stating that:

> In regard to the obviousness-type double patenting rejection, applicant's argument that multistep purification process claims in Lai et al. is not an obvious variation

> of the instant process is persuasive. And ***while the instantly claimed method is an obvious variation of the process of Lai et al. it is considered that applicant is not responsible for the delay in the prosecution of the instant application which resulted in the prior patenting of a later filed application*** to an invention derived from the instant invention. (see Ex parte Nesbit, 25 USPQ2d 1817 (1992)). Accordingly, the two-way test for obviousness double patent has been applied (see In re Braat 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991))). In support to this conclusion the examiner notes that the instant application, and its immediate parent, 06/675,298 have been subjected to extensive interparty interference and court proceedings which have delayed prosecution."

(AM-ITC 00953650-56 at 51 (emphasis added)).

However, the '179 application was filed October 27, 1987, long before the interferences commenced. Before then, Amgen had expressly and voluntarily withdrew its process claims from Ser. No. 675,298 (AM-ITC 00873642), which issued as U.S. 4,703,008. Amgen did not file the '179 application -- a continuation of Ser. No. 675,298 -- until after the issuance of the Lai '016 patent and, therefore, the PTO was not responsible for the fact that the pending claims of the '179 application (which issued as'868 patent) issued after the Lai '016 claims.

Amgen and Mr. Borun, however, did not correct the facts underlying the examiner's reason for withdrawing his rejection and, thus, the rejection was not reinstated during the prosecution of the '868 patent claims. Because of Amgen's misconduct, it has enjoyed the right to exclude the public from purifying recombinant EPO from mammalian cell culture as claimed by the Lai '016 method since in May 1987. Because the '868 patent issued over the Lai reference, the public continues to be blocked from practicing an invention where the monopoly should have ended in 2005 and, consequently, the '868 patent and the '698 patent have caused an unfair time-wise extension of the patent protection afforded to Amgen by the Lai '016 patent. Accordingly, the '868 and '698 patents are unenforceable for inequitable conduct.

Amgen's Affirmative Misrepresentations Regarding The State of the Prior Art

During the prosecution of Ser. No. 113,179 (which led to the '868 and '698 patents-in-suit), in Applicant's Second Preliminary Amendment (AM-ITC 00953205-225) dated May 24, 1988, Amgen's attorneys, in support of patentability of the pending claims, misrepresented the state of the art regarding recombinant production of what Amgen deemed human "obligate" proteins. (3/9/07 Strickland Depo. Tr. 63; 3/29/07 Elliott Depo Rough Tr. 72 (no such accepted term as "obligate" glycoprotein)). In particular, applicant argued that the pending claims were patentable and would not be obvious under 35 U.S.C. § 103 in light of prior art disclosing general recombinant techniques because the processes claimed constituted one of the first instances (if not the first instance) of the recombinant production of an in vivo biologically active human glycoprotein (AM-ITC 00953210; also AM-ITC 00953223, AM-ITC 00953277). Mr. Borun urged that:

> [N]o proper basis for rejection of the claims under 35 U.S.C. §103. In support of this position, Applicant provides the following series of remarks relating to: (1) the characteristics of human erythropoietin as an "obligate glycoprotein"; ... and (4) the lack of relevance to patentability of prior art recently ascertained and relating generally to recombinant production of glycoproteins.

(AM-ITC 00953212).

Then pending Claim 65 related "to a novel series of process steps wherein a mammalian host cell[1] capable of glycosylating the expressed polypeptides is first transformed or transfected with a DNA sequence[2] . . . .." (AM-ITC 00953210; AM-ITC 00953274; *see also* '868 patent claims). In arguing patentability, Mr. Borun urged that for an "obligate" human glycoprotein to be "provided in therapeutic quantities by recombinant means" the product would have to have the required glycosylation. He stated that: "Unlike other human glycoproteins such as the interferons and Interleukin-2, human erythropoietin was conspicuously known to be an obligate glycoprotein and no hope at all existed for isolating in vivo active material from recombinant host cells unless, at a minimum, both the issues of required polypeptide sequence and of required

glycosylation could be successfully attended to." (AM-ITC 00953214). Applicants relied on this distinction throughout the prosecution of the '868 patent claims (*see e.g.* AM-ITC 00953233 ("urges that EPO is an obligate glycoprotein and that the Yokota et al. multi CSF is not an obligate protein...."); AM-ITC 00953277 ("it appears that Applicant may have been the first to have successfully produced a human obligate glycoprotein by recombinant methods"); AM-ITC 00953646 ("As previously maintained by the Applicant, his production if in vivo biologically active glycosylated erythropoietin was among the first, if not *the* first, demonstrations of production of a biologically active obligate human glycoprotein, i.e., a human protein requiring gylcosylation for *in vivo* biological activity. Lai *et al.* claim 9 is silent on the issue of glycosylation and *in vivo* biological activity."); AM-ITC 00953699-700 ("To the extent that Yokota *et al.* might have been cited as prior an under 35 U.S.C. §102(e)/103 on the issue of obviousness of the claimed subject matter, it is also irrelevant because human M-CSF is not an obligate human glycoprotein.")) while acknowledging that tissue plasminogen activator (t-PA) also is a human obligate glycoprotein. (AM-ITC 00953221 ("Naturally occurring tPA is believed by applicant to share with erythropoietin the characteristic of being an obligate human glycoprotein.")).

In a Declaration Accompanying Petition to Make Special dated February 9, 1988, Mr. Borun represented to the examiner that:

> ***I have taken what I believe to be substantial steps to acquire knowledge of the prior art pertinent to the claims pending in the present application Serial No. 113,179.*** These steps have included the authorization of the performance of computer assisted searches through data bases reasonably assumed by me to provide information concerning pertinent prior art in the form of literature references, published U.S. and foreign patents, and foreign patent applications. I have also taken steps to familiarize myself with items of prior art which were cited in the course of PTO examination on the merits of claims in parent U.S. Patent Application Serial No. 675,298 (issued as the '008 Patent) including claims of substantially the same scope as are now pending in Application Serial No. 113,

> 179. ***Based on the above-described searching for and review of items of prior art, I believe myself to possess a "good knowledge of the pertinent prior art" with respect to the claimed subject matter and specifically those claims of application Serial No. 113,179 which relate to recombinant methods for production of erythropoietin.***

(AM-ITC 00953140 (emphasis added)). Mr. Borun also resubmitted an earlier petition to make special with respect to Ser. No. 675,298 in which he made similar representations regarding his knowledge of the prior art. (AM-ITC 00953142-82). By filing a petition to make special along with his accompanying declaration, Mr. Borun requested special treatment and induced reliance on his statements regarding the prior art.

The Petition to Make Special was granted until the next Office Action, at a minimum. (AM-ITC 00953192). There is no indication in the file history that the special status was ever revoked during the examination. Before an Office Action was issued, Mr. Borun submitted a Second Preliminary Amendment in which "to facilitate early consideration of all patentability issues", Mr. Borun caused a computer-assisted prior art search to be conducted and apprised the examiner of the results. (AM-ITC 00953219; 3/2/07 Borun Depo. Tr. 212:-213:4; *see also* AM-ITC 00953140). Amgen reported that of the references discovered during the prior art search "[t]he only reference located which appeared to relate to recombinant production of an in vivo biologically active obligate human glycoprotein was Collen et al., J. Pharm. & Expt. Therapeutics, 231, 146-152 (1984) relating to tissue plasminogen activator." (AM-ITC 00953220-221). Mr. Borun represented that the Collen reference was "accepted for publication and published well after Applicant's initial description of COS cell expression and in vivo biological activity reported in parent application Serial Nos. 561,024 and 582,185" but that "[t]he reference does not describe how the recombinant mammalian host cell expression was prepared." (AM-ITC 00953221).

Mr. Borun then reported that "[i]n a subsequent attempt to determine whether published patent applications might exist concerning mammalian cell production of recombinant tPA, a search was conducted for such applications in the Derwent World Patent Index data base." (AM-ITC 00953222). He argued that three applications located were not relevant to patentability of Ser. No. 113,179. (AM-ITC 00953222). In particular, Mr. Borun cited EP 0 093 619 ("EP '619") and included accurate applicant, publication and priority information (AM-ITC 0095322; EP '619 Application). In describing the teachings of EP '619, however, Mr. Borun affirmatively stated that EP '619 "contains no description of use of mammalian host cell expression systems for tPA production." (AM-ITC 00953222 (emphasis in original)). He represented "that the only clear mention of such systems was entirely speculative and appears in the 'Summary of Invention' at page 7:"

> In addition, depending upon the host cell, the human tissue plasminogen activator hereof may contain associated glycosylation to a greater or lesser extent compared with the native material. (Emphasis supplied).

(AM-ITC 00953222).

To appear that he was acting in good faith and with candor, Mr. Borun conceded that "[i]t is possible that an instance of successful mammalian cell expression of such an active protein might have been reported at a time prior to Applicant's work and that the report simply escaped detection in the searches described above." (AM-ITC 00953223). However, Mr. Borun expressly misrepresented the disclosure and teachings of the EP '619 application.

The EP '619 application, in fact, discloses use of vertebrate cells and mammalian cells (EP '619, pp. 15-16), CHO cells (EP '691, pp. 15-16), CHO cells deficient in DHFR activity (EP '691 p. 17), use of methotrexate with CHO cells (EP '619, pp. 17, 43), viral promoters in mammalian cells, including SV40 (EP '619, p. 16), amplification (EP '619, pp. 19, 21, 48), transfecting DHFR deficient CHO cells (EP '619, p.48), suitable growth conditions for

transfected cells (EP '619, p. 49), pharmaceutical compositions of tPA (EP '619, pp. 6, 50), and that the recombinant techniques enable "the production of sufficient quality and quantity material to initiate and conduct animal and clinical testing" (EP '619 p. 1) unlike prior art tPA "isolated from various human tissue, e.g., uterine tissue, blood, serum ... and from cell culture." (EP '619, p. 3; *see also* pp. 4, 7). Moreover, the reference claims a "composition comprising a therapeutically effective amount of human tissue plasminogen activator according to Claims 1-5 in admixture with a pharmaceutically acceptable carrier." (EP '619, claim 11; see also claims 12-15).* By 1984, animal testing plainly showed that recombinant tPA did have in vivo biological effects as disclosed by the EP '619 application, (2/21/84 Genentech Press Release, accessible at http://www.gene.com/gene/news/press-releases ("Laboratory and animal studies indicate that Genentech's t-PA is a potent, specific, clot-dissolving agent"), and in 1987, the US Food and Drug Administration approved recombinant tPA. (11/13/1987 FDA Press Release, accessible at http://www.fda.gov/bbs/topics/NEWS/NEW00191.html).

Thus, the EP '619 reference discloses that "obligate" human glycoproteins could be expressed through recombinant techniques, and supports the argument that one of skill in the art would have a reasonable expectation of success in applying those techniques to other obligate human glycoproteins such as erythropoietin. (35 U.S.C. §102(a)/§103). This directly contradicts the applicant's arguments for patentability of the process claims and would have been material to

* Amgen did not disclose counterpart U.S. 4,766,075 which issued on August 23, 1988 during the pendency of Ser. No. 113,179. The '075 patent which was filed on April 7, 1983, claims an earliest priority date of May 5, 1982 and similarly discloses a process for recombinant production of tPA. Unlike the EP '619 application which was available under §102(a)/§103, an examiner could have used the '075 patent as a basis for a §102(e)/§103 rejection. When Mr. Borun disclosed in 1994 German language references DE 33 48 289 and DE 33 48 289 (without translation) relating to production of tPA, (AM-ITC0953699; Ser. No. 113,179, Paper 44, IDS and PTO-1449) he failed to disclose the related '075 patent. (See also '868 and '698 patents, "References Cited").

a reasonable examiner. Given Mr. Borun's sworn statements regarding his knowledge of the prior art coupled with the information cited in the Amendment, the examiner had reason to rely on these representations to expedite prosecution.

Mr. Borun also cited EPO Applications 0 117 059 and 0 117 060 stating they "were assertedly based on January, 1983 U.S. filings and published in late August of 1984"; thus, implying that, unlike EP '619, those references did not even qualify as prior art to the pending claims. (AM-ITC 00953222; AM-ITC 00953699). Moreover, if the EP '059 and EP '060 applications are not prior art, then that fact supports materiality of the earlier EP '619 disclosure and Mr. Borun's misrepresentation regarding its teachings. Accordingly, based on the information Mr. Borun chose to highlight and that which he chose to omit and misrepresent, he told the examiner that the prior art provided "no demonstration of the production of an obligate human glycoprotein such as might give rise, by analogy, to any reasonable expectation of success in the practice of the methods of present claims 65-69." (AM-ITC 00953222-23).

Mr. Borun indicated that he attached EP '619 as an exhibit to Applicant's Second Preliminary Amendment (AM-ITC 00953222) and that a PTO-1449 was "scheduled to be submitted imminently". (AM-ITC 00953220). The certified file history of the '868 patent, however, does not contain any exhibits said to have accompanied the amendment in which Mr. Borun misrepresented the disclosure of the EP '619 application. The certified file history shows that a PTO-1449 form was filed in September 1988, nearly 4 months after the Second Preliminary Amendment and after receiving an Office Action subsequent to Mr. Borun's misrepresentation of the prior art and in which the examiner relied on prior art references different from the references purportedly explained by Mr. Borun to the PTO. The referenced PTO-1449 form is not part of the certified file history but the accompanying IDS specifically

discusses the Colleen reference again. (AM-ITC 00953281; *see also* ITC-AM 00953698). The IDS, however, does not expressly identify EP '619 or correct Mr. Borun's earlier misrepresentations pertaining to its teachings and disclosure. (AM-ITC 009530280-81).

The only two references specifically identified as pertaining to obligate human glycoproteins were reference X-28 (relating "to common alpha subunit of human glycoprotein hormone in mouse cells") and the Colleen reference -- neither of which is EP '619. All the other references submitted "did not actually relate to the recombinant expression of cloned genes," "did not relate to expression in cells capable of glycosylation," "did not relate to human glycoproteins" or "did not relate to human glycoproteins for which glycosylation was necessary for in vivo biological." (AM-ITC 00953280-81). Given this information, there is only two possible conclusions either (1) EP '619 was included among the references cited on the PTO-1449 form and Mr. Borun's colleague -- Mr. Gruber -- again misrepresented its disclosure and teachings or (2) EP '619 was not include on the PTO-1449 form for the examiner's consideration.

In any event, no steps were taken to correct Mr. Borun's earlier misrepresentations regarding EP '619. Rather, Amgen's counsel -- Mr. Odre -- purported to attach a Table to Applicant's Reply dated September 27, 1988 accompanying the IDS stating:

> Attached hereto as Exhibit "D" is a Table describing the proteins which are the subject of expression in the references reviewed for the purposes of Applicant's previous submission. As will be apparent from consideration of the Table, ***no public reports of recombinant expression of an obligate human glycoprotein appeared before the December 13, 1983 filing of parent application*** Serial No. 561,024.

(AM-ITC 00953277)(emphasis added). Given the November 9, 1983 publication of EP '619, this statement was a misrepresentation of the state of the art regarding obligate human glycoproteins.

After the September 1988 IDS was submitted -- along with the Reply that also did not correct Mr. Borun's misrepresentations regarding its teachings and disclosure (AM-ITC 00953273-78) -- Examiner Tanenholtz issued a Notice of Allowability for pending process claims 65-69 (AM-ITC 00953308) but Amgen continued with prosecution.

An additional IDS was submitted in January 1994, more than 4 ½ years after Mr. Borun's misrepresentation with respect to EP '619. The reference was listed as "B4" along with 374 other references apparently submitted to the PTO (AM-ITC 00953609-35), and was identified by a source code as "References of record in the parent applications of U.S. Pat. Appln. No. 07/113,179," "References of record in U.S. Pat. Appln. No. 07/113,179, which were not previously listed on Form PTO-1449" and "Defendants' 35 U.S.C. §282 Notice from the Amgen Inc. v. Chugai and G.I., C.A. No. 87-2617-Y, District Court proceedings in Boston, MA regarding parent U.S. Patent No. 4,703,008" (AM-ITC 00953609-10) insinuating to the new examiner -- Examiner Hodges -- that the reference had already been substantively considered and overcome in proving patentability of the pending claims.

There is no indication in the parent files of Ser. No. 113,179, Ser. No. 113, 179 itself, or the *Amgen v. Chugai* opinion that EP '619 was ever substantively considered with respect to the patentability of any process claim. Furthermore, Amgen argued that patentability of the process claims was not addressed by any determination of patentability of '008 patent claims: "In proceedings before the Board of Patent Appeals and Interferences, separate interferences were drawn for the DNA-related subject matter of U.S. 4,703,008 and the production process subject matter claimed herein."; "In proceedings before the International Trade Commission and the subsequent appeal to the Court of Appeals for the Federal Circuit, it was judicially determined that the claims of U.S. Patent No. 4,703,008 did not 'cover' recombinant production processes

within the meaning of 19 U.S.C. §337." (AM-ITC 00953697). Thus, under applicant's arguments (whether correct or not), Mr. Borun knew that the relevance of EP '619 in determining the patentability of the pending process claims previously had not been determined by the Board of Appeals, the ITC, or the Federal Circuit.

Nonetheless, Mr. Borun and Amgen continued to rely upon his earlier misrepresentation regarding EP '619 to for patentability over the prior art as well as with respect to a double-patenting rejection. In the last substantive filing -- without specifically mentioning the patent number (forcing any interested party to scour the file history to identify the reference) or correcting his earlier misrepresentation regarding its teachings -- Mr. Borun argued to a new examiner, Examiner Martinell, that "the state of the art in production of recombinant glycoproteins as of late 1983" did not render the pending claims obvious and that the reference was already considered by the previous examiners. (AM-ITC 00953698 ("Evidence of non-obviousness was provided in the Applicant's Preliminary Amendment dated May 24, 1988 (Paper No. 8) and in Applicant's Reply dated September 26, 1988 (Paper No. 11); ("The then-cited publications correspond to references B4, B7, B8, C35, C89, C94, C234 and C280 of the Information Disclosure Statement considered by Examiner Hodges on February 9, 1994.") AM-ITC 00953700 ("The Yokota *et al.* Reference Is Not Relevant to Obviousness-type Double Patenting.")). Examiner Martinell allowed the pending claims to issue as the '868 patent without further action. (AM-ITC 00953708). Related process claims also issued in the '698 patent as a result of Amgen's misconduct in securing the '868 claims and its continued silence regarding the relevant state of the art. (AM-ITC 00898335-37; AM-ITC 00898343-53; AM-ITC 00898390).

Not only did Mr. Borun and Amgen misrepresent the state of the art for "obligate" glycoproteins and mislead the examiner with respect to the relevance of other human proteins to

the pending process claims, they also omitted material art regarding recombinant production of other human glycoproteins, including human interferons. The '179 file history shows that Mr. Borun and Amgen were aware of and tracking patents and publications relating to these other human proteins. (*e.g.*, AM-ITC 00953220-21 ("As set out in greater detail in the PTO-1449 Statement scheduled to be submitted imminently, the references generally dealt with ... recombinant expression of human glycoproteins which are not obligate glycoproteins."); AM-ITC 00953612 (U.S. 4,757,006 disclosing human factor VIII:C); AM-ITC 00953711 (McCormick *et al.*, "Regulated Expression of Human Interferon Genes in Chinese Hamster Ovary Cells," *DNA* 2(1). 86 Abst 86 (1983); McCormick *et al.*, "Inducible Expression of Amplified Human Beta Interferon Genes in CHO Cells," *Mol. Cell. Biol.*, 4(1):166-172 (1984)); Ser. No. 113,179, Paper 44, IDS and PTO-1449; Taniguchi *et al.*, "Structure and expression of a cloned cDNA for human interleukin-2," *Nature*, 285:628-34 (1983)) The file history also makes plain that -- until Amgen's misrepresentation regarding the purported distinction of "obligate" glycoproteins and the state of the art was relied upon -- at least Examiner Tanenholtz considered the recombinant production of glycoproteins other than erythropoietin to be material to the pending process claims, and Amgen and Mr. Borun were aware of the examiner's position. (AM-ITC 00953228 (citing Yokota U.S. 4,695,542 disclosing production of GMCSF); AM-ITC 00953276 (characterizing Yokata as disclosing multi-CSF or IL-3 (interleukin-3)); *see also* AM-ITC 00953693).

With respect to human interferon, Amgen failed to disclose McCormick *et al.* U.S. 4,966,843 ("the '843 patent") despite its knowledge of McCormick's work. The '843 patent entitled "Expression of Interferon Genes In Chinese Hamster Ovary Cells", on its face, claims priority to Ser. No. 438,991 ("the '991 application") filed November 1, 1982 -- a full year before

the earliest priority date for the asserted Lin patents. Furthermore, a declaration submitted during examination of the '991 application and resubmitted during examination of the application that led to the '843 patent, discloses the date of conception for the claimed invention was December 9, 1981 and that recombinant interferon was expressed by approximately April 1982. ('843 patent file history, 9/6/84 Declaration Under 37 CFR §1.131). Had the '843 patent been disclosed, the examiner would have known about the earlier priority date based on the '991 application and could have rejected the pending process claims in light of McCormick. (MPEP § 706.02 (regarding §102(e)/§103)).

Both the '843 patent and the '991 priority application disclose that human interferon β is a glycoprotein by chemical measurement of its carbohydrate content and that production in animal host cells were "expected to be glycosylated and in conformation closest to that of native human IFNs". ('991 application, pp. 2-3; '843 patent, col. 1:49-50, col. 2:3-8). The '991 application, in fact, discloses use of mammalian cells ('991 application, p. 4), CHO cells ('991 application, p. 10), CHO cells deficient in DHFR activity ('991 application, pp. 9, 11-12), use of methotrexate with CHO cells ('991 application, p. 15), viral promoters in mammalian cells, including SV40 ('991 application, pp. 8, 9), amplification with methotrexate ('991 application, p. 15), transfecting DHFR deficient CHO cells ('991 application, pp. 12-14), suitable growth conditions for transfected cells ('991 application, pp. 14-15), pharmaceutical compositions of interferon ('991 application, p. 10), and that the disclosed recombinant techniques produce glycosylated products "substantially identical in structure, properties and confirmation to native IFNs" ('991 application, p. 17) unlike prior art interferons that "exhibit[] altered physical properties which may be due in part to the absence of glycosyl residues." ('991 application, p. 3; '843 patent col. 2:1-3). Moreover, the '991 application claims a method for production of

interferon "where in said interferon is glycosylated" ('991 application, claims 13 and 14; '843 patent claim 15).

Accordingly, misrepresentations and omissions regarding prior art references which disclose processes for recombinant production of glycoproteins render at least the '868 and '698 patents unenforceable for inequitable conduct.

Amgen Did Not Disclose the Baron-Goldwasser Clinical Study

In the 1980's Drs. Baron and Goldwasser -- while Amgen consultants who worked closely with the company on its recombinant erythropoietin project -- conducted human clinical trials with urinary erythropoietin ("the Baron-Goldwasser clinical study"). Amgen has admitted that it neither submitted to the Patent Office the actual scientific data, clinical submissions and reports to the FDA, or described the Baron-Goldwasser clinical study in papers, responses to office actions or IDS submitted to the examiners. And evidence shows that individuals involved with drafting and prosecuting the patents-in-suit, including Dr. Lin, Dr. Egrie and Mr. Odre were aware of the Baron-Goldwasser clinical study. (AM-ITC00557514-27; AM-ITC00245727-29; AM-ITC 00084770-80; 12/1/99 Egrie Depo. Tr. 409-412; 3/9/07 Strickland Depo. Tr. 332-333; 6/7/00 Lin Trial Tr. 947-948; 6/8/00 Lin Trial Tr. 1095). Mr. Borun spoke to Dr. Goldwasser regarding his work with erythropoietin vis-à-vis the Lin patents. (2/14/07 Goldwasser Depo. Tr. 167-168; 11/14/89 Goldwasser Depo. Tr. 289-290, 294).

The information from the Baron-Goldwasser clinical study would have been important to a reasonable examiner. For example, the patents-in-suit disclose that:

> [T]o the extent that polypeptide products of the invention share the in vivo activity of natural EPO isolates they are conspicuously suitable for use in erythropoietin therapy procedures practiced on mammals, including humans, to develop any or all of the effects herefore attributed in vivo to EPO, e.g., stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass

> changes, stimulation of hemoglobin C synthesis (see, Eschbach, et al., supra) and, as indicated in Example 10, increasing hematocrit levels in mammals.

(e.g. '422 patent, col. 33:11-22). This language indicates that the claimed invention is used in "therapy" to produce "any or all" of the following "effects": stimulation of reticulocyte response, development of ferrokinetic effects, erythrocyte mass changes, stimulation of hemoglobin, and increasing hematocrit levels.

Furthermore, in a Request for Reconsideration Amgen's attorney -- Watson Scott -- stated to Examiner Stanton that:

> The specification indicates several potential therapeutic uses for the claimed invention. More particularly, the specification at pages 86-87 recites the following:
>
> > Similarly, to the extent that polypeptide products of the invention share the in vivo activity of natural EPO isolates they are conspicuously suitable for use in erythropoietin therapy procedures practiced on mammals, including humans, to develop any or all of the effects herefore attributed in vivo to EPO, e.g., stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis (see, Eschbach, et al., supra) and, as indicated in Example 10, increasing hematocrit levels in mammals. Included within the class of humans treatable with products of the invention are patients generally requiring blood transfusions and including trauma victims, surgical patients, renal disease patients including dialysis patients, and patients with a variety of blood composition affecting disorders, such as hemophilia, sickle cell disease, physiologic anemias, and the like.
>
> It is believed that ***these sentences from the specification and others provide a clear and definite description of*** the uses for which the claimed erythropoietin compositions would be ***therapeutically effective.***

(AM-ITC 00899171 (emphasis added). Thus, Amgen, including at least Mr. Watt who was involved in prosecuting the '422 patent, was aware that Amgen had interpreted the passage at column 33, lines 11-22 of the specification as corresponding to the "therapeutically effective" claims limitations in the pending claims. (See also AM-ITC 0089917, AM-ITC 00899179).

The information disseminated in Amgen regarding the Baron-Goldwasser study, including the actual patient data, shows that this information was relevant to the claims being prosecuted in the PTO. For example, Amgen, including at least Mr. Odre, was aware of the pharmaceutical composition (including human serum albumin) to used in the study as well as the patient results. (AM-ITC 00573893-903). At least Drs. Lin, Egrie, Strickland and Browne -- who were all involved in the drafting and prosecution of the patents -- were aware of the Baron-Goldwasser clinical study and Amgen used the study "as a guideline" to determine dosing for administering EPO. (AM-ITC 00557514-27). At least Dr. Lin was aware that Dr. Baron reported that with administration of urinary erythropoietin "each patient showed a mild to modest increase in reticulocyte number", "two of the three patients showed increased numbers of nucleated red cells/1000 bone marrow cells and the disappearance of radio-iron from plasma was shortened in two of the three individuals" and "one of the three patients showed an increase in red cell mass following the treatment program." (AM-ITC 00245727-29; see also AM-ITC 00084770-80; AM-ITC 00849306-41). To the extent that Dr. Lin and other individuals affiliated with Amgen now testify during litigation that they did not believe the results of the clinical studies, that is not a legitimate reason nor a credible excuse for withholding information from the examiner in light of Lin's own specification and the contemporaneous documents that show the therapeutic effects reported by Baron and Goldwasser.

Amgen and its attorneys were aware that they could not patent what was already disclosed in the prior art, including erythropoietin and pharmaceutical compositions comprising erythropoietin, and pharmaceutical compositions containing EPO and human serum albumin. (See, e.g., AM-ITC 00899124; AM-ITC 00899160 (rejection over Miyake urinary EPO); AM-ITC 00899161 ("the EPO recited in the claims reads directly upon natural isolates and the basis

of the instant rejection as explained above properly establishes that the claimed invention would have been *prima facie* obvious.")). Indeed, Amgen's attorneys argued that from the prior art of record "there is no indication that a diluent such human serum albumin would be required to prepare a pharmaceutical composition with erythropoietin." (AM-ITC 00899174). Likewise, the PTO told Amgen that source limitations alone would not confer patentability on products described in the prior art. (See, e.g., AM-ITC 00899419). Thus, there was every reason not to disclose the Baron-Goldwasser clinical study, and but for Amgen's conduct, the claims of the '422 patent would not have issued.

With the knowledge of the Baron-Goldwasser clinical study, however, Amgen prosecuted claims including, for example:

- "An erythropoietin-containing, pharmaceutically acceptable composition wherein human serum albumin is mixed with erythropoietin." (AM-ITC 00899084).
- "A composition according to claim 61 containing a therapeutically effective amount of erythropoietin." (AM-ITC00899084).
- "A composition according to claim 61 containing a therapeutically effective amount of recombinant erythropoietin." (AM-ITC00899084).
- "A pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is purified from mammalian cells grown in culture." ('422 patent, claim 1).
- "A pharmaceutically-acceptable preparation containing a therapeutically effective amount of erythropoietin wherein human serum albumin is mixed with said erythropoietin." ('422 patent, claim 2).

To the extent that Amgen relies on the interference files to show that the Baron-Goldwasser clinical study was somehow disclosed to the examiner(s), any purported discussion which may have mentioned the study was buried within the interference filings, did not consist of the actual documents that disclose the clinical results or set forth contemporaneous analysis of the results and, therefore, the information was effectively withheld from the examiner(s). The files for Interferences 102,096, 102,097 and 102,334 contain over 18,000 pages. Without

Amgen pointing out any information regarding the clinical study, the examiner would not have known the relevance of the study or where within the mountain of interference submissions to find any purported information.* And, as stated above, Amgen has admitted that it did not disclose the data or clinical protocols even in the context of the interferences.

The IDS statements filed by Amgen after the interferences make clear that the documents disclosing the Baron-Goldwasser clinical study were not considered "references of record", nor was any exhibit or deposition purportedly disclosing the Baron-Goldwasser clinical study cited as such. Furthermore, when Amgen's attorneys discussed prior art erythropoietin disclosed by Goldwasser during an interview with Examiners Stanton and Martinell (AM-ITC 00899441), the discussion was limited to partially purified erythropoietin preparations obtained from sheep plasma, not the clinical study relating to human urinary EPO. (AM-ITC 00899474).

Accordingly, the '422 patent is unenforceable for inequitable conduct.

Amgen's Affirmative Misrepresentations and Omissions Regarding COS rEPO

In addition to the conduct discussed above, in order to obtain product claims to erythropoietin -- a naturally occurring hormone -- and to overcome patentability rejections, Amgen inserted various limitations into its pending claims, including "having glycosylation

* Relevant to each and every basis of inequitable conduct set forth is the fact that the patents-in-suit are based upon multiple CIP and continuation applications, with protracted prosecutions containing numerous, lengthy responses, declarations and IDS Statements submitted by Amgen, multiple Examiner Interviews, and multiple interferences. Examiners in the biotechnology filed, however, generally spent approximately 20 hours examining an application. (e.g. U.S. GAO, Biotechnology Backlog of Patent Applications, GAO/RCED-89-120BR, "Average Time Spent Per Patent Application", p. 20). In that time an examiner is charged with reading the application, reading the submitted prior art, searching for and reading prior art, comparing that prior art to the application, writing office actions, reading and responding to the responses to office actions, conducting interviews and issuing claims. An examiner does not have the time to sift through voluminous interference files or IDS references looking for information that may or may not be there and, thus, relies on the candor of applicants in particularly pointing out important information.