Exhibit 8

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' SUPPLEMENTAL RESPONSES AND OBJECTIONS TO PLAINTIFF 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.

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.

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.

INTERROGATORIES

Subject to and without waiving its General Objections, Roche objects and responds to Amgen's interrogatories 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.

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-

* 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).

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 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,

* 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).

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.

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. <u>Therefore, it is submitted that if Lin was the first</u>

> 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.

which differs from that of human urinary erythropoietin" (*e.g.* '933 patent; AM-ITC 00941452; AM-ITC 00941511; AM-ITC 00941545), "has glycosylation which differs from that of human urinary erythropoietin" (e.g. '080 patent; AM-ITC 00868072; AM-ITC 00868083), "said product has a higher molecular weight than human urinary EPO as measured by SDS-PAGE (*e.g.* '933 patent; AM-ITC 00941545) and "having an average carbohydrate composition which differs from that of naturally occurring [human] erythropoietin." (e.g. '933 patent; AM-ITC 00941041; AM-ITC 00941108; AM-ITC 00941165; AM-ITC 00941188; AM-ITC 00941208, AM-ITC 00941212; AM-ITC 00941546).

During prosecution, like Amgen during litigation, the applicant maintained that the claimed inventions covered recombinant erythropoietin expressed in a variety of host cells including both CHO and COS cells. (e.g. AM-ITC 00941111; AM-ITC 00941548; see also AM-ITC 00953641 ("Applicant has disclosed the production of ... human species erythropoietin in monkey (COS) and Chinese Hamster Ovary (CHO) cells."). Ser. No. 113, 178 and the related continuation applications included dependent claims "wherein the host cell is a mammalian cell" or "a non-human mammalian cell" ('933 patent; AM-ITC 00941109; AM-ITC 00941166, AM-ITC 00941208; AM-ITC00941213; AM-ITC 00941453; AM-ITC 00941511; AM-ITC 00941511), "wherein the host cell is a COS cell" (AM-ITC 00941109; AM-ITC 00941166) and "wherein the host cell is a CHO cell." ('933 patent, AM-ITC 00941109; AM-ITC 00941166; AM-ITC 00941208; AM-ITC00941213; AM-ITC 00941453; AM-ITC 00941511; AM-ITC 00941546). Mr. Borun explained that dependent claims "further characterize products of the present invention in terms of their derivation from eucaryotic host cell expression ... particularly in mammalian host cells (64) such as COS (65) and CHO (66) cells" (AM-ITC 00941111). Accordingly, to support and prove patentability of the independent claims with limitations to

glycosylation, molecular weight and average carbohydrate composition, differences between human EPO and recombinant EPO from COS and CHO cells needed to be shown.*

Examiner Kushan stated that "the sites and extent of glycosylation and how they 'differ' from native EPO should be pointed out." (AM-ITC 00941093). He further explained that:

> This protein is inherently identical to the claimed EPO by virtue of the same amino acid sequence (or an allelic variant thereof) and the same type of biological activity. The recombinant protein has not been shown to behave in a distinct and unobvious manner with respect to the naturally occurring EPO, and in any case the claims clearly encompass the naturally produced EPO shown by the cited art. ***The burden of proving the claimed rEPO distinct and unobvious over the cited prior art is shifted to the applicant***.

(AM-ITC 00941095-96 (emphasis added)).

By Amendment and Reply, Amgen stated that:

> As is apparent from consideration of independent claim 41, ***the subject matter herein claimed is seen to comprise Applicant's novel glycoprotein preparations*** having amino acid sequence characteristics in common with naturally occurring human erythropoietin isolated from urine, ***having carbohydrate composition characteristics different from those of naturally occurring erythropoietin*** and nonetheless having the glycosylation-requiring in vivo biological activity (promoting reticulocyte and red blood cell production) characteristics of naturally occurring human erythropoietin.

(AM-ITC 00941111 (emphasis added)). Furthermore it was urged that:

> Applicant was the first to provide for a glycoprotein which is both different from previously isolated urinary erythropoietin in its glycosylation and yet sufficiently like the natural product (previously isolated in the art) in terms of its glycosylation to allow it to fill the long-felt need (unsatisfiable by urinary

* It is telling that Mr. Borun eventually dropped the dependent claim specifically claiming COS host cells without comment or explanation to the examiner, and not until after the examiner relied on the Strickland Declaration. The only conclusion is that Mr. Borun was aware of the data that showed there is no difference between COS rEPO and human urinary EPO, and abandoned the claim. Nonetheless, the omitted and misrepresented information is material because remaining claims cover rEPO expressed by COS cells. (e.g. '933 patent; '080 patent; 3/5/2007 "Amgen's Claim Construction Brief" at 6 ("Dr. Lin's specification discloses how to manipulate a range of host cells, including mammalian cells ... to produce a therapeutically effective EPO composition.")

> isolates) for life-sustaining human therapeutic agents for, e.g., the anemia associated with dialysis in renal failure patients.
>
> The precise nature of ***the differences in the carbohydrate structures of products of the present invention and urinary-derived human erythropoietin are only now starting to be understood, as evidenced by the results of the experimental procedures detailed in the attached Declaration of Thomas W. Strickland***. Briefly put, the procedures demonstrate that the urinary erythropoietin is heterogeneous in terms of glycosylation, that the same is true of recombinant erythropoietin preparations of the present invention, and that, ***most importantly, the two products are clearly distinct from each other in terms of glycosylation***.
>
> Having provided the public with its first knowledge concerning the fact that a glycoprotein can exist which is simultaneously different in carbohydrate composition from urinary source erythropoietin and yet sufficiently like it in glycosylation to allow for in vivo biological activity, no impermissible vagueness attends the recitation of these unique and readily ascertainable characteristics in a patent claim."

(AM-ITC 00941114-5 (emphasis added)). Responding to rejections under §102 and §103, Amgen stated:

> ***Confirmation of these assertions of novelty is found in the attached Declaration of Thomas Strickland*** which provides detailed description and analysis of the differences in carbohydrate structure between FDA clinical lot preparations of recombinant erythropoietin according to the present invention and human urinary erythropoietin isolates as represented by samples actually obtained by Miyake et al. in the work forming the basis for the publication, as well as urinary erythropoietin samples obtained by means of a specified modification of the Miyake et al. procedure. ...
>
> The work described in the Strickland Declaration and that of the publication cited by Strickland, as well as the results set out in the Sasaki et al. publication noted by the Examiner, ***stands as testimony to the differences between Applicant's products and those of Miyake et al***. In sum, ***Applicant's products are indeed novel***.
>
> Against a background wherein the prior art had noted the essential nature of sialic acid residues for in vivo biological activity, it could hardly be characterized as within the reasonable expectation of an ordinarily skilled artisan (i.e., obvious) that ***Applicant could call into existence the glycoprotein products herein claimed -- glycoproteins which have a carbohydrate composition conspicuously-different from that of human urinary erythropoietin glycoprotein isolates***, but which nonetheless have sufficient amino acid sequence and

> glycosylation similarities to allow them to possess the essential in vivo biological activity of naturally occurring erythropoietin.

(AM-ITC 00941116-17 (emphasis added); *see also* 11/23/99 Borun Depo. Tr. 125:12-126:21.)

Rather than submit information comparing the glycosylation, molecular weight and average carbohydrate composition of human urinary EPO versus recombinant EPO expressed in COS cells -- which was necessary to support the independent claims as well as dependent claims to mammalian cells and COS cells -- the Strickland Declaration disclosed information pertaining only to the comparison of human urinary EPO versus recombinant EPO expressed in CHO cells. (AM-ITC 00941121 ("The r-HuEPO for use in the experimental procedures was prepared in accordance with the general procedures described in Example 10 of USSN 113,178 ...."); see also, e.g., Strickland Depo. Tr. 155-156, 208-217, 293-311, 208:14-16 ("My declaration . . . doesn't have any information on COS-cell EPO"); 215:12-14 ("I don't think I could infer anything about COS-cell EPO from the information in [my] declaration.")).

Under Section 1001 of Title 18 of the United States Code Strickland represented that:

> 11. The above analysis of r-HuEPO and u-EPO demonstrate that the differences shown by the isoelectric focusing experiments, specifically, the more acidic nature of the u-EPO isoforms compared to the r-HuEPO isoforms, is due to the differences in carbohydrate composition, in particular carbohydrate structure, of r-HuEPO and u-EPO. ***This analysis indicates that recombinant erythropoietin as described by Serial No. 113,178 has a different carbohydrate composition than naturally occurring urinary erythropoietin***.

(AM-ITC 00941134 (emphasis added)). However, the recombinant erythropoietin as described by Ser. No. 113,178 includes COS r-EPO, which Amgen knew had not shown differences in glycosylation, molecular weight and average carbohydrate composition. The Strickland Declaration intentionally omitted this information and focused solely on supposed differences between CHO r-EPO and human urinary EPO. For example, the Strickland Declaration omitted

at least the following information regarding the similarity in glycosylation, molecular weight and average carbohydrate composition of COS rEPO compared to human urinary EPO:

- Egrie *et al*., Characterization Of Recombinant Monkey And Human Erythropoietin, *Proc Clin Biol Res.* 1985;191:339-50: "As seen in Figure 5, recombinant human EPO produced in COS1 cells has a molecular weight of 34,000 daltons and migrates identically to the human urinary standard, suggesting that both the recombinant and native EPO are glycosylated to the same extent." (See 3/27/07 Egrie Depo. Tr.79-81, 86-90).
- Egrie *et al.*, Abstract (1984) from 10th Annual Fredrick Stohlman Memorial Symposium on Stem Cell Physiology, Boston, MA, October 2, 1984: "By Western analysis, the recombinant erythropoietin has a molecular weight of 34,000 daltons and migrates identically to the human standard erythropoietin, indicating that the expressed protein is glycosylated to the same extent as the native hormone."; "By all criteria examined, the recombinant monkey and human erythropoietin appear identical to the native hormone."
- Egrie *et al*., Presentation (1984) from 10th Annual Fredrick Stohlman Memorial Symposium on Stem Cell Physiology, Boston, MA, October 2, 1984 (AM-ITC 01073032-42): "MW and migration of recombinant EPO is identical to EPO standard indicating recombinant EPO is glycosylated to the same extent as the native hormone."; "CONCLUSION: COS CELLS TRANSFECTED WITH THE HUMAN EPO GENE PRODUCE AND SECRETE FULLY GLYCOSYLATED EPO WHICH MIGRATES IDENTICALLY TO THE HUMAN EPO STANDARD."
- Egrie, Presentation Transcript "Cloning of Human & Monkey EPO" (1984) from Hemoglobin Switching Meeting, Airlie House, Virginia, September 1984 (AM-ITC 00557610-16; 3/27/07 Egrie Depo. Tr. 70-71, 79-81): "In order to determine the size of the recombinant erythropoietin, we characterized the COS-cell expressed EPO by Western analysis. ... This band has a MW of 34,000 daltons + migrates identically to the human EPO standard. ... These expts show that the recombinant mK + hu Erythropoietin are the same size as the native hormone which suggests that both the recombinant + native hormones are glycosylated to the same extent." (AM-ITC 00557614-15). "These sequences have been expressed in both COS + CHO cells + the expressed erythropoietin has been shown to be immunologically identical to the native hormone. It has the same MW as the native hormone [illegible] suggesting that it is glycosylated to the same extent." (AM-ITC 00557616). (See also AM-ITC 00557617-23).

The Egrie articles apparently were not submitted in any of the patents-in-suit and plainly are not listed on the face of the patents as "references cited". (e.g. AM-ITC 009414122-49*; AM-ITC 00868126-55*; '933 patent; '080 patent).

* This IDS, which was submitted after the '344 Interference, submitted "references of record" in the parent applications of Ser. No. 07/113,178, Ser. No. 07/113,179, "references of record" in Ser. No. 07/113,178 which were not previously cited on a PTO-892 form, references from the §282 Notice and exhibits admitted in *Amgen v. Chugai* (D. Mass.) and "references of

Furthermore, prior to filing the CIP application Ser. No. 675,298, Dr. Egrie had provided laboratory notebook pages to Mr. Borun (11/10/99 Egrie Depo Tr. 335-336) -- who drafted the Lin specification (3/2/07 Borun Depo. Tr. 14:2-13; 11/23/99 Borun Depo. Tr. 21:21-23:15; 9/06/2000 Trial Tr. 2831:2-4; 2/5/2002 Borun Trial Tr. 239:12-240:9) -- that showed COS rEPO was no different than human urinary EPO. Indeed, she plainly and unequivocally concluded that "human EPO produced by COS cells have the same molecular weight as native urinary EPO (Goldwasser's EPO). This result indicates that the recombinant EPO is glycosylated to the same extent as the native protein." (AM-ITC 01072494; AM-ITC 01072497; 09/6/2000 Trial Tr. 2845:6-17). While at various times Mr. Borun has testified that he did not recall seeing the Egrie input file until years after the application was filed -- the exact time depending on which time he was asked -- (11/23/99 Borun Depo. 71:21-73:11, 90:16-91:6; 9/6/2000 Borun Trial Tr. 2848:7-22, 2853:3-4; 2863:3-8) his testimony is not credible. Mr. Borun asked for the information (9/6/00 Trial Tr. 2835:17-2836:8; 2/5/2002 Borun Trial Tr. 263:12-15; AM-ITC 01072474) and Dr. Egrie provided the information before Mr. Borun drafted and submitted the CIP application Ser. No. 675,298 (11/8/99 Borun Depo Tr. 325, 334-336; 2/5/2002 Borun Trial Tr. 264:20-270:25, 282:20-283:2, 283:20-284:3; 11/10/99 Egrie Depo. Tr. 325; AM-ITC 01072476). Mr. Borun had the Egrie data in his files. (9/6/2000 Trial Tr. 2837:22-2838:3; 2/5/2002 Borun Trial Tr. 248:3-14). It is Mr. Borun's practice to review information that he has requested. (2/5/2002 Borun Trial Tr. 248:22-249:18) and there is no legitimate reason to believe that he did not follow his normal practice. Moreover, Dr. Lin declared under oath in a submission to the PTO that the

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record" from European Opposition Proceedings regarding the foreign counterpart EP 0148 605). The Egrie articles are not included as being a "reference of record."

* This IDS also "identifies all art of record" from SN 07/113,179 and SN 08/487,774, but does not include any of the Egrie articles.

studies conducted by Dr. Egrie are set forth in Example 10 of the patent application. (AM-ITC 00295812; see also 11/23/99 Borun Depo. 65:11-21). In any event, Mr. Borun admits that he was aware of the Egrie data when the applications that led to the '933 and '080 patent were still pending. (11/23/99 Borun Depo. 83:21-85:13, 91:7-16; 9/6/2000 Borun Trial Tr. 2863:3-8). Nonetheless, the Egrie data was not submitted to the examiner in any response to an Office Action and was not included on any IDS submitted to the examiner.* (9/6/2000 Borun Trial Tr. 2864:5-8, 2865:6-14).

As a consequence of the information chosen to be disclosed by the Strickland Declaration and that which withheld, Examiner Kushan stated that:

> Applicant has shown through the declaration of Strickland and via the disclosure of Takeuchi et al [regarding CHO rEPO] that there is a difference in the overall carbohydrate composition between the naturally occurring and recombinant species. ... The proof of a distinction in the physical attributes of the naturally isolated and recombinant species is sufficient to overcome the rejections over 35 USC 102.

(AM-ITC 00941151-52). Amgen, however, argued commercial success, long-felt need and other secondary considerations in an attempt to prove patentability under §103. (AM-ITC 00941159; AM-ITC 00941169-72; AM-ITC 00941182). Nonetheless, applicant continued to argue that "Recombinant erythropoietin is different from naturally occurring erythropoietin (for a description of the differences, see the response filed December 5, 1988)" (AM-ITC 00941168) and continued to omit material information regarding COS rEPO covered by the pending claims (AM-ITC 00941165-66; AM-ITC 00941179 ("Applicant's claim encompass erythropoietin produced recombinantly in any eucaryotic cell line which has an average carbohydrate composition which differs from naturally occurring human EPO, and which possess a particular

* Compare AM-ITC 00941422-449 submitting 2 boxes of documents purportedly including exhibits from *Amgen v. Chugai* (but not the Egrie file) with Mr. Borun's testimony that the Egrie file was an exhibit in that action. (TKT Trial Tr. at 2863:9 to 2864:4).

in vivo activity when administered to humans.")). Thus, the examiner was left with the misimpression that both recombinant EPO from COS cells and recombinant EPO from CHO cells differed from urinary EPO.

Applicant was fully aware that Examiner Kushan had relied on the partial information provided with respect to CHO rEPO in removing his then pending rejections. As Examiner Kushan explained:

> ***Applicant has proven that human EPO isolated from urine is distinct from the EPO produced recombinantly according to the instant disclosure***. ...
>
> Applicant must provide for a distinction between the lymphoblastoid derived EPO and the instantly claimed recombinant species. ***Applicant is encouraged to file a declaration in the form of the previous declaration of Strickland, which provided evidence of a distinction between the urinary and recombinant species***.

(AM-ITC 00941180-81 (emphasis added)).

Again, however, applicant did not submit the omitted information regarding COS rEPO to the examiner, instead opting to once again point to the defective Strickland Declaration to overcome a prior art rejection based on Sugimoto:

> In the response filed December 5, 1988, ***the Strickland Declaration established the difference between human produced urinary erythropoietin and the recombinant glycoprotein***. As discussed with the Examiner during the interview, urinary-derived erythropoietin-is active in vivo. There is no teaching in Sugimoto et al. that the carbohydrate composition of the product produced is different from urinary-derived erythropoietin. Nor is there any teaching that the Sugimoto et al. product is the same as the recombinant glycoprotein claimed herein."

(AM-ITC 00941192 (emphasis added)). In response, the examiner dropped his rejection.

In the following continuation application, Mr. Borun also submitted an IDS dated April 8, 1994 along with two boxes of references (AM-ITC 00941422-50). Among the 394 references submitted by Mr. Borun was WO 86/03520 ("PCT '520"), which Amgen represented was a reference of record in the parent applications of Ser. No. 113,178. (AM-ITC 00941422). There is, however, no previous IDS in the certified file histories of the parent applications that

disclosed this reference, there is no IDS in the '178 application disclosing the reference, and the reference is not listed on the earlier '008 patent as a reference cited. The reference was cited in Ser. No. 113,179 (which led to the '868 patent), but that co-pending application is not directly related to Ser. No. 113,178. Furthermore, in prosecuting Ser. No. 113,179, again, Amgen had represented that the reference was already of record in the parent applications (AM-ITC 00953609; AM-ITC 00953612), which it apparently was not.

Given Mr. Borun's misrepresentation there would be no reason for Examiner Martinell to focus on the PCT reference because it would have appeared that it was already considered by at least one other examiner and that the reference was not deemed important to patentability. (MPEP §704.01, MPEP §1214.04) (full faith and credit to the prior examiner's search)). Furthermore, given the earliest priority date, the filing date and the publication date of the PCT application, there was no reason for the examiner to give more than a cursory look past the cover sheet of the reference.

However, WO 86/03520 discloses that:

> By Western blotting, using a polyclonal anti-EPO antibody, the ***EPO produced by COS cells has a mobility on SDS-polyacrylamide gels which is identical to that of native EPO prepared from human urine*** (Example 8). Thus, the extent of glycosylation of COS-1 produced EPO may be similar to that of native EPO.

(WO 86/03520, pp. 1026-27 and Fig. 6 (emphasis added)).

Moreover, Applicant and Dr. Strickland were aware of the PCT '520 reference during the prosecution of the applications leading to the '933 and '080 patents. In February 1992, Dr. Strickland had submitted a declaration opposing EP 0 411 678 (AM-ITC 00326183-98), which has the same disclosure as PCT '520. (3/9/07 Strickland Depo. Tr. 275-277). In his declaration, Dr. Strickland addressed molecular weight and the monosaccharide content of rEPO produced by Amgen, and concluded that the "values are within the range of experimental and analytical

error". This declaration was not submitted to the PTO, nor did Dr. Strickland's earlier declaration that was submitted discuss the impact of experimental and analytical error in determining differences/similarities in glycosylation, molecular weight and average carbohydrate composition of recombinant EPO compared to human urinary EPO.

An Examiner Interview Summary Record indicated that "Applicant intends to submit declaration evidence to show that r-EPO differs in glycosylation from any of the naturally occurring EPOs known as of the effective filing date of the instant application ***and even from the naturally occurring EPOs known since.***" (AM-ITC-00941497 (emphasis added)). This apparently refers to "the January, 1994 expert statement of Dr. Richard Cummings (Exhibit B herein) as submitted in proceedings before the European Patent Office in counterpart European Patent EP 0 148 605" (AM-ITC 00903254-488), which is not found in the certified file history. Once again, a declaration submitted on behalf of the applicant, omitted material information regarding COS rEPO.

The declaration, again, focuses primarily on CHO rEPO. The only mention of COS rEPO (AM-ITC 00822949 ¶6.2) is in passing and relies on information lifted directly from the Lin application which, as discussed above, ignores conflicting test results set forth by Dr. Egrie's internal work at Amgen. Dr. Cumming did not include any published literature regarding COS rEPO but directed the examiner's focus, yet again, to CHO rEPO and other references regarding EPO expressed in BHK, C127 mouse fibroblast, Namalwa and BHK-21. To the extent that Dr. Cummings mentioned "2 articles by Egrie" cited by Dr. Conradt, he does not give any identifying information such as title, publication or date so that examiner could independently obtain the articles and the articles were not attached as exhibits to his declaration (AM-ITC 00903238-448). Moreover, the Egrie articles referenced by Dr. Cummings may have related to

CHO rEPO, not COS rEPO, as discussed in more detail below. Mr. Borun also did not provide the opposing Conradt Declaration (or any other declarations opposing Amgen's viewpoint which it knew about) to the examiner.

To the extent that Dr. Cummings discussed the "2 articles by Egrie", he misrepresented the conclusions presented in those references. Although it is not clear from the submission to the PTO which of the Egrie articles Dr. Cummings referred to, as discussed above, each Egrie article concluded that COS rEPO and human urinary EPO "migrate identically." But, that is not what he and Mr. Borun told the examiner. Instead, the declaration states that:

> 17.4.2 Dr. Conradt cites to two articles by Egrie et al. which show several SDS-PAGE and Western blot analysis on rEPO and uEPO. Again, the gels in these articles show that the rEPO and uEPO samples migrate to similar regions, but they do not precisely comigrate. The gels would suggest the samples were similar but not identical, and any comments in the articles must be interpreted with the gels in view.

(AM-ITC 00903276). Obviously, however, Dr. Egrie and/or her co-authors had the "gels in view" and still made the conclusion in each paper that COS r EPO and uEPO "migrates identically" -- in direct contradiction to Dr. Cummings statements. Furthermore, neither Egrie articles were submitted to the PTO in an IDS and none is cited on the face of the patents as a reference cited.

Along with the Cummings Declaration, Mr. Borun also argued that: "As confirmed by Takeuchi article cited by the Examiner, the glycosylation of recombinant EPO products is different from that of urinary EPO." (AM-ITC-00941515-16). The Takeuchi article, however, relates to CHO rEPO, not COS rEPO. (AM-ITC 00903340-42).

When prosecution resumed after Interference 102,334, Examiner Fitzgerald allowed pending claims 76-83 (AM-ITC 00941409; AM-ITC 00941413), but Mr. Borun elected to continue prosecution without letting the claims issue. Subsequently, when Mr. Borun was

unable to get a different examiner -- Examiner Martinell -- to allow pending claims, Amgen urged that: "New claim 99 has a text identical to claim 76 of prior U.S. Application Serial No. 113,178. Claim 76 was allowed prior to filing of parent U.S. Application Serial No. 08/202,874 and its text was identical to the sole Count in Fritsch v. Lin, Interference No. 102,334." (AM-ITC-00941537; AM-ITC 00941547). However, claim 99 did not have text identical to either claim 76 or the sole Count. Furthermore, Mr. Borun added claims to "glycosylation which differs from that of human urinary erythropoietin" and "said product has a higher molecular weight than human urinary EPO as measured by SDS-PAGE." (AM-ITC 00941544-51). Mr. Borun and Amgen's in-house counsel -- who had been practicing for years -- were aware of PTO rules stating that "a claim noted as allowable shall thereafter be rejected only after the proposed rejection has been submitted to the primary examiner for consideration of all the facts and approval of the proposed action. Great care should be exercised in authorizing such a rejection". (See also MPEP §704.01 (regarding "full faith and credit")). They plainly used those rules advantageously. The Examiner allowed those claims, as well as dependent claims, to issue without further rejection. (AM-ITC 00941562-65).

Subsequently, based on the actions of applicants during prosecution of the '933 patent claims, Examiner Martinell also allowed the '080 patent to issue without rejection over any prior art, including claims to a glycoprotein that "has glycosylation which differs from that of human urinary erythropoietin". (AM-ITC 00868083-88; AM-ITC00868157-59).

To the extent that Amgen relies on the '334 Interference file to show that material information was submitted to the PTO, that does not negate the fact that those documents were buried within its interference filings, effectively withheld from the subsequent examiner(s) and, thus, material information was omitted from the prosecution file while other information

highlighting purported differences between the claims and the prior art were misrepresented to the examiner. Moreover, the IDS statements filed by Amgen after the Interference make clear that the references discussed herein were not considered "references of record".

The '344 Interference file alone comprises approximately 5,500 pages of documents focusing on CHO rEPO, and the file for the consolidated Interferences 102,096, 102,097 and 102,334 is over 18,000 pages. Any alleged statement regarding COS rEPO does not qualify as proper disclosure. Nor does it negate an intent to deceive by misdirecting the examiner from material information regarding COS rEPO to focus instead on CHO rEPO. If anything, it shows a pattern of misconduct by applicant and Amgen to hide behind the technical procedures of the PTO rather than fulfill its duty of good faith and fair dealing with the examiners here. Amgen took advantage of the limited hours that an examiner is allotted and the sheer volume of documents contained in the prosecution files (including related interferences) and forced the examiners to scour thousands of pages to rack down material information that Amgen knew about and should have brought to the forefront. Amgen also exploited the fact that multiple examiners were responsible for the examination of the applications leading to the patents-in-suit.

Furthermore, only §102 and certain sections under §112 were at issue in the ' 334 Interference, not patentability pursuant to §103. (e.g. *Fritsch v. Lin*, 21 USPQ2d 1739, 1742 (BPAI 1991); AM-ITC 00832914-15 ("The Fritsch et al motion is based on Section 102(b), not 103.")). Similarly, information submitted and allegedly considered in the '334 Interference was considered only in the context of the claim limitation "having an average carbohydrate composition which differs from that of human urinary erythropoietin" (Count 1, AM-ITC 00941235). The Interference did not substantively address the patentability of the other limitations "having glycosylation which differs from that of human urinary erythropoietin", "has

glycosylation which differs from that of human urinary erythropoietin", or "said product has a higher molecular weight than human urinary EPO as measured by SDS-PAGE. (AM-ITC 00941407 ("Claims 76-83 ... were the only claims considered by the BPAI and Court.")). Indeed, those claim limitations did not appear in any filed claims until years after the Opinion of the Board of Patent Appeals and Interferences. (AM-ITC 00941237).

Importantly, the focus of the arguments presented in the Interference file was the difference between CHO rEPO and human urinary EPO, not COS rEPO. Thus, a subsequent examiner would quickly dismiss the idea of looking closely at the Interference record for information regarding COS rEPO. For example:

- AM-ITC 00295811 (emphasis added):

> 5. My patent application involved in the subject interference indicates that recombinant human erythropoietin (rHuEPO) of my invention has an average carbohydrate composition which differs from that of EPO in a partially purified pooled source human urinary EPO preparation obtained from Dr. Goldwasser. This is based in part on the work done by Dr. Egrie with ***recombinant human EPO expressed from CHO cells*** and on other work on carbohydrate analysis done by Dr. Robert K. Yu, both acting at my request.

- AM-ITC 00295812 (emphasis added):

> 7. Dr. Egrie showed by Western blot analysis and SDS-PAGE that CHO cell produced rHuEPO migrated differently than the pooled urinary EPO present in a partially purified sample provided by Dr. Eugene Goldwasser. Studies conducted by Dr. Egrie involving digestion of the ***CHO cell produced rHuEPO*** and the pooled human urinary EPO with carbohydrate digesting enzymes indicated that the difference in migration, which is indicative of difference in apparent molecular weight, resulted from a difference in carbohydrate moieties. These studies are set forth in Example 10 of my patent application.

- AM-ITC 00295814 (emphasis added):

> The results of carbohydrate analysis provided to me by Dr. Egrie (see paragraph 7 above) and Dr. Yu, by November 30, 1984, indicated that the <u>in</u> <u>vivo</u> biologically active ***recombinant EPO product expressed by CHO cells***, had an average

carbohydrate composition which was different from the pooled human urinary EPO obtained from Dr. Goldwasser.

- AM-ITC 00295815 (emphasis added):

9. I am advised that the count of the interference in which I am involved reads as follows:

Interference No. 102,334

A non-naturally occurring glycoprotein product of the expression in a non-human eucaryotic host cell of an exogenous DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin said product possessing the in vivo biological property of causing human bone marrow cells to increase production of reticulocytes and red blood cells and having an average carbohydrate composition which differs from that of naturally occurring human erythropoietin.

10. I confirm that the ***rHuEPO produced by CHO cells transfected with the human genomic EPO gene meets all of the limitations of the count of Interference No. 102,334.*** Dr. Browne, acting at my request, carried out the expression in CHO cells of the rHuEPO.

- AM-ITC 00339456 (emphasis added):

the Strickland Declaration unambiguously demonstrates that ***rEPO produced according to Example 10 of the Lin application and uEPO differ*** in their monosaccharide composition ...

- AM-ITC 00361603 (emphasis added):

(25) The in vivo biologically active ***rHuEPO that was expressed in CHO cells*** by May of 1984 was shown by Dr. Egrie and subsequently by others to have an average carbohydrate composition that differed from that of a partially purified pooled source human urinary EPO provided by Dr. Goldwasser. ...

- AM-ITC 00832911 (emphasis added):

The conspicuously missing "fact" is that the carbohydrate composition of the prior art urinary EPO is the same as the carbohydrate composition of Lin's recombinant EPO as exemplified by his ***Example 10 expression product of the human EPO gene in Chinese Hamster Ovary (CHO) cells***.

- AM-ITC 00832911 (emphasis added):

> 2. Yes, Lin submitted a declaration by Dr. Strickland under Section 132 and the 102(b) ***rejection was withdrawn upon directing the Examiner's attention to differences in carbohydrate composition between the Lin Example 10 product and the prior art product***.

- AM-ITC 00832913 (emphasis added):

> There has been no showing or representation by Fritsch et al that the average carbohydrate composition of urinary EPO and ***Lin's CHO cell-expressed recombinant EPO of Example 10*** are in fact identical in all aspects.

- AM-ITC 00832914-15 (emphasis added):

> The Fritsch et al. motion is based on Section 102(b), not 103. To bar patentability, Section 102 requires identity of subject matter, not a generalized similarity. To overcome a rejection under § 102, one need only show that the claimed subject matter is different. Lin has clearly shown this. ***Fritsch et al has submitted no evidence to show that urinary EPO and Lin's Example 10 EPO are identical***, in particular with respect to carbohydrate.

- AM-ITC 00832918 (emphasis added):

> However, it is significant that Cumming presents no evidence of his own to confirm his position that urinary EPO is identical in its carbohydrate composition to ***Lin's Example 10 EPO***.

- AM-ITC 00832919 (emphasis added):

> Finally, it is noted that the Fritsch at al argument really bypasses the fundamental point, namely, ***Lin's CHO cell-expressed recombinant human EPO as obtained in Example 10***, shows a different average carbohydrate composition from a pooled source of human urinary EPO. ... It has not been shown that Lin's Example 10 product does not meet the requirements of the Lin claims or the count. Fritsch at al have not, therefore, sustained their burden.

- AM-ITC 00832920 (emphasis added):

> The ***CHO-expressed recombinant product*** obtained by Lin as exemplified in his disclosure (for instance, Example 10) meets the claim limitation to the effect that the recombinant product is different in terms of average carbohydrate composition from naturally-occurring EPO (LR 105).

The opinion from the Board of Patent Appeals and Interferences makes plain that they -- like the examiner -- focused on CHO rEPO and not COS rEPO. (*Fritsch v. Lin*, 21 USPQ2d 1739 (BPAI 1991) (discussing purported evidence of alleged differences in "average carbohydrate

composition" including specific mention of CHO cells, Example 10, the *Takeuchi* reference and Amgen's PLA (all based on CHO rEPO))). Likewise, the opinion makes no mention of any Egrie articles or other reference regarding COS rEPO.

But for Amgen's misconduct conduct at least claims 1 and 6 of the '933 patent and claim 1 of the '080 patent would not have issued. Accordingly, the '933 patent and the related '080 patents are unenforceable for inequitable conduct.

Amgen's Affirmative Misrepresentations and Omissions Regarding CHO rEPO

In addition to the information outlined above, Amgen also withheld and misrepresented information regarding CHO rEPO. Applicant's attorneys affirmatively told the examiner that: that "Applicant intends to submit declaration evidence to show that r-EPO differs in glycosylation from any of the naturally occurring EPOs known as of the effective filing date of the instant application and ***even from the naturally occurring EPOs known since.***" (AM-ITC-00941497 (emphasis added). Thus, Amgen affirmatively represented that it would provide information regarding prior art uEPO purified using the Miyake method (e.g. "Goldwasser's EPO) as well as uEPO from other sources (e.g. Lot 82 and Alpha Therapeutics). Instead, Amgen offered the Cummings Declaration as discussed above.

Dr. Egrie's data showing that there were no differences when Lin's CHO rEPO was compared to Lot 82 and Alpha Therapeutics urinary EPO was not provided in either (1) the Cummings declaration or (2) any filings submitted by the applicants in response to office actions. (AM-ITC01072481; AM-ITC 01072486 (both showing "CHO(2) + Lot 82 same size", "α Therapeutics - is same size as CHO + Lot 82"). Amgen relied solely on supposed differences between Goldwasser uEPO (AM-ITC 01072499) in drafting the language of the patent

specification and ignored the conflicting results based on comparisons to Lot 82 and Alpha Therapeutics urinary EPO. (2/5/2002 Borun Trial Tr. 298:10-299:8, 300:19-301:2).

Furthermore, the Cummings declaration cherry-picked information relied upon. As discussed above in relation to COS rEPO, Cummings hastily mentioned two articles by Egrie *et al.* but he did not give any information to identify the which of the Egrie articles he was referring to so that the examiner could independently review the articles. The two Egrie articles that discuss CHO rEPO concluded that:

- Egrie *et al.*, 1986, Characterization and Biological Effects of Recombinant Human Erythropoietin, *Immunobiol*., vol. 172, pp. 213-224 (1986): "By Western analysis, ***the recombinant and human urinary EPO migrate identically***."; "As seen in Figure 4, purified rHuEPO migrates identically with an apparent molecular weight of approximately 36,000 daltons, suggesting that both molecules are glycosylated to the same extent."
- Eschbach *et al.* Correction Of The Anemia Of End-Stage Renal Disease With Recombinant Human Erythropoietin, *NEJM* 316:73-78 (1987) (Egrie, co-author): "Complete analysis of human urinary erythropoietin and recombinant human erythropoietin has demonstrated that the hormones have the same amino acid sequence. In addition, ***the carbohydrate portion*** and the immunologic and biologic properties ***of the natural urinary and recombinant hormones are indistinguishable***."

However, that is not what he and Mr. Borun told the examiner. Instead, in direct contradiction to the Egrie articles, the declaration states:

> 17.4.2 Dr. Conradt cites to two articles by Egrie et al. which show several SDS-PAGE and Western blot analysis on rEPO and uEPO. Again, the gels in these articles show that the rEPO and uEPO samples migrate to similar regions, but they do not precisely comigrate. The gels would suggest the samples were similar but not identical, and any comments in the articles must be interpreted with the gels in view.

(AM-ITC 00903276). Furthermore, neither of these Egrie articles was submitted to the PTO in an IDS and none is cited on the face of the patents as a reference cited. Likewise, the 1984 Egrie Presentation (AM-ITC 01073033 ("MW and migration of recombinant EPO is identical to EPO standard indicating recombinant EPO is glycosylated to the same extent as the native hormone.")

also was not submitted to the examiner and is not cited as a reference cited or a reference of record in an IDS.

In addition, Dr. Cumming's citation to the Brown article regarding CHO rEPO is merely a passing reference with respect to O-glycosylation of EPO in support of his argument regarding the Nimtz et al (1993) reference. The articles he relied on to show differences between rEPO and uEPO were clearly summarized in table form for the examiner (AM-ITC 00903273) and did not include the Browne article, implying that the Browne article was not relevant to the main thrust of his declaration. Neither Dr. Cummings not Amgen pointed out that the Browne article undercut the arguments he was making based on other references. Important and contradictory data and conclusions set forth in Browne include:

> Human urinary EPO and CHO-cell derived r-hEPO migrate identically in SDS-polyacrylamide gels indicating that both molecules are glycosylated to a similar extent. ... The carbohydrate composition of r-hEPO was essentially the same as that of urinary EPO (T.W. Strickland et al., in prep) ...
>
> Shown in Figure 4 are the results of a deglycosylation experiment that indicates that both r-hEPO and urinary EPO contain both N-linked and O-linked carbohydrates in similar amounts. Both r-hEPO and urinary EPO were analyzed by Western blot analysis after sequential gycosylase digestion. ***Figure 4 (lanes 1 and 5) shows urinary EPO and r-hEPO, respectively, prior to treatment***. After treatment with endoglycosidase F which removes N-linked carbohydrate, ***the apparent molecular weight of both r-hEPO and urinary EPO is shifted to approximately 19,500 with a minor band at about 18,400*** (lanes 2 and 6). Following further treatment, first with sialidase (lanes 3 and 7) and then by O-glycanase (lanes 4 and 9), which remove O-linked carbohydrate, ***both r-hEP0 and urinary EPO migrated as a single band with an apparent molecular weight of 18,400***. Although the presence of N-acetylgalactosamine had not been detected previously (Dordal et al. 1985). These results demonstrate that urinary EPO, as well as r-hEPO contains O-linked carbohydrate. In addition, direct carbohydrate analysis of endoglycosidase-F treated r-hEPO yields galactose, sialic acid, and N-acetyl galactosamine, confirming the presence of O-linked carbohydrate (T.W. Strickland et al., in prep). As shown in Figure 4, the proportion of EPO containing O-linked carbohydrate is comparable in urinary EPO and r-hEPO.

(AM-ITC 00903452). Mr. Borun did not submit the Browne reference in the IDS which included "references of record" in the prosecution (AM-ITC00941422-449) and the article is not cited as considered by the examiner(s) in allowing the '933 patent. Furthermore, the reference is not cited on the face of the '933 patent as a reference cited ('933 patent). However, in later applications the reference was submitted indicating its materiality was appreciated by the applicants. (e.g. '080 patent). Likewise, the Board of Appeals apparently did not substantively consider or rely on the Egrie articles or the Browne article. *Fritsch v. Lin*, 21 USPQ2d 1739, 1742 (BPAI 1991).

Similarly, Amgen and its attorneys did not disclose Vapnek *et al.*, "Comparative Studies of Natural and Recombinant Erythropoietin," *Banbury Reports 29:Therapeutic Peptides and Proteins*, 241-56 (1988) (see, e.g., '933 patent and '080 patent "References Cited") which reported "no differences in structure have been observed" between CHO rEPO and urinary EPO. The article also reports that treatment with Endo F, neuraminidase and O-glycanase "demonstrate that both urinary and recombinant human Epo contain sialic acid, O-linked carbohydrate, and three N-linked carbohydrate chains. Further characterization of the fine structure of the carbohydrate chains is currently being carried out (A. Kubota et al., unpubl.). Initial results indicate that both contain oligosaccharides of the same structure."

Additionally, in order to receive approval for its CHO r-EPO drug, Amgen made statements to the FDA that directly contradict the positions Amgen took in arguing patentability of its EPO claims to the PTO. Significantly, these statements were not submitted to the examiner of the '933 patent. (See AM-ITC 00092853 ("Where it is possible to compare r-HuEPO and u-HuEPO, the two materials were shown to be identical within the error of the methods."; "The most relevant findings are the overall similarity of the oligosaccharide structures and the

demonstration that all of the carbohydrate structures in r-HuEPO are also found in u-EPO."); AM-ITC 00092884; AM-ITC 00092981-83). Nor did Amgen explain to the examiner(s) that purported differences in glycosylation and carbohydrate composition were not due to differences between CHO rEPO and urinary EPO, but because of different purification techniques in certain instances and variability and error in testing techniques. These documents and information were not submitted to the examiners.

Furthermore, after Amgen learned of the error in its reporting of the carbohydrate analysis of CHO rEPO and urinary EPO in example 10 ('933 patent 28:51-67), it did not make that error known to the various examiners or the public by disclosing the mistake in any response or amendment in the file history. But for Amgen's misconduct conduct at least claims 1, 2 and 6 of the '933 patent and claim 1 of the '080 patent would not have issued. Accordingly, the '933 patent and the related '080 patents are unenforceable for inequitable conduct.

Amgen's Affirmative Misrepresentations and Omissions Regarding Molecular Weight

In addition to the information outlined above regarding COS rEPO and CHO rEPO (hereby incorporated), in 1995 Mr. Borun presented for the first time a claim requiring that "said product has a higher molecular weight than human urinary EPO as measured by SDS-PAGE." (AM-ITC 00941545), and the claim was allowed without a rejection or any amendment. ('933 patent). Relevant literature, as well as Lin's specification, acknowledged that human urinary erythropoietin is a glycoprotein with a molecular weight of approximately 34,000 daltons (*e.g.* '933, col. 5:48-52 ("Erythropoietin, an acidic glycoprotein of approximately 34,000 dalton molecular weight, may occur in three forms: α, β and asialo. The α and β forms differ slightly in carbohydrate components, but have the same potency, biological activity and molecular weight."); AM-ITC 00987639-49 ("The human asialo hormone has an apparent molecular

weight of 34,000 in SDS, whereas the native form has an apparent molecular weight of 39,000.")). Dr. Egrie also had measured the molecular weight of various urinary EPOs and found that Goldwasser's uEPO "is 34,000 MW + Lot-82 EPO - ~35-36". (AM-ITC 01072482; 4/15/91 Egrie Depo. Tr. 562-565).

Dr. Strickland, however, filed a declaration in May 1994 in related foreign proceedings that showed rEPO produced in accordance with Lin's Example 10 falls between 31,000 daltons and 45,000 daltons as measured by SDS-PAGE. (AM-ITC00312260-71; 3/9/07 Strickland Depo. Tr. 277-280). Clearly 31,000 daltons is not a "higher molecular weight than human urinary EPO as measured by SDS-PAGE", yet the Amgen never submitted this information or declaration to the U.S. examiner(s). In that same proceeding, Cilag GmbH, an Opposing Party (AM-ITC 00312411) -- along with Kirin-Amgen, Inc. an assignee of the '933 patent-in-suit -- filed a declaration by Dr. Thomas Heckler ("Exhibit 4") stating that: "The molecular weight of the purified r-HuEPO band shown in Figure 5 was calculated by comparison of its migration to that of the protein standards and r-HuEPO reference standard. The r-HuEPO migrated identically to the reference standard (which had a molecular weight of 34,000 daltons) ...." (AM-ITC00311606). Dr. Goldwasser also filed a declaration ("Exhibit 1") in which he reported that the apparent molecular weight of urinary erythropoietin as measured by SDS-page was first reported as 39,000 daltons and later reported as 34,000 daltons. (1/23/93 Declaration of Eugene Goldwasser Ph.D., ¶21). Amgen "relie[d] without limitation upon Citations 1 through 7a and Exhibits 1-17 presented by Opponent I herein, Cilag GmbH." (AM-ITC 00312411-12). This information was not submitted to the U.S. patent examiners.[*]

[*] Attorneys for Cilag and Johnson & Johnson kept at least in-house Amgen attorneys, Messrs. Watt and Odre, apprised of developments in Europe. (e.g. AM-ITC 0312283; AM-ITC 0312291-92). Mr. Watt was a corporate officer of Kirin-Amgen, Inc. (e.g. AM-ITC 00898341).

Likewise, its own Product License Agreement, which was not submitted to the PTO, shows that Amgen's rEPO does not have a higher molecular weight than urinary EPO. (AM-ITC 00092870; AM-ITC 00092880). Indeed, the product label states that Amgen's rEPO product "has a molecular weight of 30,400 daltons... ." (See AM-ITC 00092249-60 (10/30/87 Proposed Package Insert); Physician's Desk Reference (44th ed. 1990) at 616; AM-ITC 00601553-60 (6/29/94 Product Label for Epogen®); 3/09/2007 Product Label for Epogen® and Procrit® available at www.accessdata.fda.gov). Neither the draft or approved Product Label was submitted to the examiner(s).

Furthermore, in September 1985, when the applications leading to the '933 patent were still pending, Amgen submitted its Notice of Claimed Investigational Exemption for Recombinant-Human Erythropoietin (r-HuEPO) to Office of Biologics Research and Review Center for Drugs and Biologics at the Food and Drug Administration (AM-ITC 00091218) in relation to seeking approval of its CHO rEPO product. The application was assigned to Amgen's attorney, Mr. Odre, who also prosecuted the applications that resulted in the '933 patent. In that document, Amgen represented that: "The r-HuEPO migrates identically to the pure urinary hormone with an apparent molecular weight of ~ 36,000 daltons" in SDS-polyacrylamide. (AM-ITC 00092135, 00092210-11). Thus, showing that Amgen's CHO rEPO covered by the '933

Indeed, Messrs. Odre, Watt and Borun, as well as Drs. Strickland, Egrie and Goldwasser attended the oral arguments for the foreign proceedings relating to EP 209 539. (AM-ITC 00312754). Additionally, written submissions by Kirin-Amgen, Inc. included confidential information provided by Amgen, Inc. (e.g. AM-ITC 00312455-73) and declarations provided by Amgen employees. (e.g. AM-ITC 00312260-71; AM-ITC 00312441-45). The Strickland, Goldwasser and Heckler declarations were all in the possession of Amgen's patent counsel at Marshall, Gerstein & Borun, including Mr. Borun. (See, e.g., February 20, 2007 Third Party Marshall, Gerstein & Borun LLP's Objections and Responses to Subpoena *Ad Testificandum* and *Duces Tecum*, Objections and Response to Request No. 1; March 27, 2007 Letter from Ross to Rycroft).

patent does not have a "higher molecular weight than human urinary EPO as measured by SDS-PAGE." Again, Amgen did not submit this information to the examiner(s).

In addition, as discussed above, Amgen and its attorneys were aware that the claim was not patentable. Dr. Egrie had concluded that "human EPO produced by COS cells have the same molecular weight as native urinary EPO (Goldwasser's EPO)" (AM-ITC 01072494; AM-ITC 01072497; 11/10/99 Egrie Depo. Tr. 340-342) and that CHO rEPO was the same as Lot 82 and Alpha Therapeutics urinary EPO. (AM-ITC 01072481-86). (*See also* 11/23/99 Borun Depo Tr. 79:3-80:7). Applicant also failed to properly submit the Egrie papers and presentation which showed that COS rEPO and CHO rEPO did not have a higher molecular weight than human urinary EPO as measured by SDS-PAGE. Likewise, as discussed above, key information from the Browne article regarding molecular weights was not properly presented to the examiner(s). Nor was Vapnek *et al*., which concluded that "both rh-Epo and urinary Epo have an apparent molecular weight of approximately 36,000" disclosed to the examiner(s).

Omitting this information is especially egregious given applicant's representation that Amgen would submit evidence to show that r-EPO differs in glycosylation -- and, thus, apparent molecular weight -- "even from the naturally occurring EPOs known since" the filing of the patents. But for Amgen's misconduct, at least claim 2 of the '933 patent would not have issued. Accordingly, the '933 patent and the related '080 patent are unenforceable for inequitable conduct.

Amgen's Prosecution of Claims Rejected By Different Examiners

Amgen's patents-in-suit issued from one of two co-pending lines of applications, based on Ser. No. 113,178 (the '178 application) and Ser. No. 113,179 (the '179 application). The

'178 line ultimately led to the '080 and '933 patents, while the '179 line ultimately led to the '868, '698, '422 and '349 patents.

On numerous occasions during the prosecution of these co-pending lines of applications, the examiner in one line of co-pending applications issued rejections to claims that were substantially similar to claims that Amgen was prosecuting in the other co-pending line. The existence and grounds for such rejections in one co-pending line constituted highly material information that Amgen had a duty to disclose. A prior rejection of a substantially similar claim refutes, or is inconsistent with the position that those claims are patentable. An adverse decision by another examiner, therefore, is material under the Rule 56.

The patents-in-suit are unenforceable because individuals associated with the filing and prosecution of these patents, in arguing for the patentability of pending claims in one line of applications knowingly took positions inconsistent with highly material arguments that examiners raised against the patentability of substantially similar claims in the other co-pending line of applications, but nonetheless knowingly and intentionally failed to disclose those rejections.

Amgen's intent to deceive the PTO is further evidenced by the fact that at least applicant's attorneys -- Mr. Odre and Mr. Borun -- were both involved throughout the prosecution of the '178 and '179 lines of applications, and therefore, had intimate knowledge regarding the proceedings of both lines of applications. (e.g. AM-ITC 00941082-88; AM-ITC 00941146; AM-ITC 00941553; AM-ITC 00953196-202; AM-ITC 00953233-34; AM-ITC 00953689). In addition, Mr. Borun was intimately involved in and was, therefore, aware of material details of the prosecution of the parent applications which led to the '008 patent. (AM-ITC 00953135-74).

In prosecution of the '179 application, Amgen submitted a Second Preliminary Amendment (AM-ITC 00953205-25) canceling all pending claims and entering five new claims 65-69. Among these the only independent claim (65) recited "a process for the preparation of an *in vivo* biologically active glycosylated polypeptide comprising the steps of:

> (a) growing a mammalian host cell which is capable of effecting post-translational glycosylation of polypeptides expressed therein and which is transformed or transfected with an isolated DNA sequence encoding a polypeptide having a primary structural conformation sufficiently duplicative of that of naturally occurring human erythropoietin to allow possession of the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, or the progeny thereof, under nutrient conditions suitable to allow, in sequence,
>
> > (i) transcription within said host cell of said DNA to mRNA in the sequence of transcription reactions directed by the nucleotide sequence of said DNA;
> >
> > (ii) translation within said host cell of said mRNA to a polypeptide in the sequence of translation reactions directed by the nucleotide sequence of said transcribed mRNA;
> >
> > (iii) glycosylation within said host cell of said polypeptide in a pattern directed by the amino acid sequence of said translated polypeptide and sufficiently duplicative of the pattern of glycosylation of naturally occurring human erythropoietin to allow possession by the translated glycosylated polypeptide product of the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells; and
>
> (b) isolating the glycosylated polypeptide so produced.

(AM-ITC 00953207-08). The dependent claims further characterized the claimed process in terms of host cell expression of cDNA (68) or genomic DNA (69) sequences, particularly in a CHO cell (66) or COS cell (67). (AM-ITC 00953208).

In the first Office Action dated August 3, 1988 (AM-ITC00953227-31), Examiner Tanenholtz rejected the pending claims to a host cell expression process for making a glycosylated recombinant EPO (rEPO) as obvious and unpatentable over Yokota *et al*. (US Pat.

No. 4,695,542) which taught "a process as claimed herein differing only in using mammalian DNA sequence that encodes a different polypeptide" and "growing a mammalian host cell which is capable of effecting post-translational glycosylation of polypeptides expressed therein ...." (AM-ITC 00953228). He also noted the Yokata *et al.* "teach the production and in fact claim the production of a gylcosylated product." (AM-ITC 00953229). The rejection was also in view of Gething *et al*. 1982 (Nature, vol. 300, pp. 598-603), which indicated "that eukaryotic cells innately possess the property of glycosylating proteins." (AM-ITC 00953229). Examiner Tanenholtz noted that "it would be expected that where one expresses the cDNA gene encoding erythropoietin using the Yokota et al. procedures the resulting erythropoietin would necessarily be glycosylated." (AM-ITC 0953229).

In this same time period, in the co-pending '178 application, Amgen sought to prosecute substantially similar claims directed to the product of the process described by its pending '179 application claims. Examiner Tanenholtz was not involved in the '178 prosecution, which was before Examiner Kushan. (e.g. AM-ITC 00941146). In particular, in its December 1, 1988 Amendment and Reply (AM-ITC 00941106-18), applicant amended claim 41 and added new claims 61-66 directed to a human erythropoietin glycoprotein product "having a primary structural conformation and glycosylation sufficiently duplicative of that of a naturally occurring human erythropoietin to allow possession of the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells" and further characterized as a product derived "from eukaryotic host cell expression (61) of exogenous cDNA (62) or genomic DNA (63) sequences, particularly in mammalian host cells (64) such as COS (65) and CHO(66) cells." (AM-ITC 0941108-09).

Applicant argued for patentability in light of previous prior art rejections -- none of which was based on either Yokata and/or Gething -- stating:

> [I]t could hardly be characterized as within the reasonable expectation of an ordinarily skilled artisan (i.e., obvious) that Applicant could call into existence the glycoprotein products herein claimed -- glycoproteins which have a carbohydrate composition conspicuously different from that of human urinary erythropoietin glycoprotein isolates but which nonetheless have sufficient amino acid sequence and glycosylation similarities to allow them to possess the essential in vivo biological activity of naturally occurring erythropoietin.

(AM-ITC 00941117).

The substantial similarity of these pending ’178 claims to the pending process claims of the ’179 application (and Amgen’s awareness of that fact) is plainly evident through the Reply to Examiner Tanenholtz’ August 3, 1988 Office Action in the ’179 prosecution. There, Amgen argued that pending claims 65-69 were directed to:

> a novel series of process steps wherein a mammalian host cell [including such non-human, non-kidney cells as COS and CHO cells as specified in claims 66 and 67] capable of glycosylating the expressed polypeptides is first transformed or transfected with a DNA sequence [including, e.g., cDNA and genomic DNA as specified in claims 68 and 69] encoding a specifically delineated polypeptide, i.e., one having a sufficient amino acid sequence homology to natural human erythropoietin to allow it to qualify, amino acid sequence-wise, for potential in vivo biological activity. (The DNA reagent employed in the transformation/transfection process is itself the novel and unobvious subject matter of claim 7 of U.S. Patent 4,703,008 and the resulting host cells are as recited in claim 24 of the Patent).

(AM-ITC 00953274).

Applicant’s characterization of its pending ’179 claims strikingly demonstrates that its ’178 application claims were directed to nothing more than the inherent product of the ’179 process claims 65-69. Aware of the high materiality of Examiner Tanenholtz’s rejection in the ’179 prosecution to the substantially similar claims then pending in the ’178 prosecution, Amgen knowingly and intentionally failed to disclose that rejection, or the basis for that rejection to Examiner Kushan in the ’178 prosecution.

The failure to disclose Examiner Tanenholtz' August 3, 1988 rejection to Examiner Kushan during the prosecution of the '178 claims gained greater significance in view of Amgen's subsequent actions in the '178 prosecution and its subsequent reliance on product-by-process claims. On February 10, 1989, Examiner Kushan issued a Final Office Action rejecting all the pending claims on several grounds. (AM-ITC 00941148-58). Among the rejections, Examiner Kushan objected to the claimed description of the glycoprotein product as having "glycosylation sufficiently duplicative of that of a naturally occurring human erythropoietin" because "The manner in which applicant has attempted to characterize the degree and extent of glycosylation of the r-huEPO does not particularly point out what the actual glycosylation comprises." (AM-ITC 00941149). Notably, however, Examiner Kushan never raised the prior art arguments that Examiner Tanenholtz had raised as to the obviousness of the process used to make the claimed rEPO product, nor did he raise the Yokota or Gething references that Examiner Tanenholtz had cited.

In response, Amgen replaced all pending claims with new claims 67-75, which defined the claimed product solely through the process through which it was made. (AM-ITC 00941165-72) In particular, Amgen acknowledged that:

> All product claims in the subject application are ***now product-by-process claims***. Independent claim 67, and thus all of the pending claims, specifically ***define the erythropoietin of the subject invention as a "glycoprotein product of the expression of an exogenous DNA sequence in a eucaryotic host cell...."*** These product-by-process claims are presented in an effort to positively recite the physical properties of recombinant erythropoietin, and to further define the product of the subject invention since the recombinant erythropoietin claimed cannot be precisely defined except by the process by which it is produced.

(AM-ITC 00941167-68) (emphasis addeed). Applicant once again did not disclose that Examiner Tanenholtz had rejected the its related process claims over the prior art.

Throughout the remainder of the '178 prosecution, Amgen continued to argue the novelty of its product-by-process claims to a glycosylated erythropoietin knowing that its arguments for patentability were wholly inconsistent with Examiner Tanenholtz's rejection of the process claims as obvious and continued to hide that rejection from the attention of the '178 examiners.

In an Amendment dated July 11, 1989 (AM-ITC 00941188-97), applicant kept all its product-by-process claims pending, amending only claim 67 to specify that the claimed product of host cell expression was one produced through a process using "a non-human eucaryotic host cell" (AM-ITC 00941188), in order to distinguish the claimed erythropoietin product from the erythropoietin product produced by using a human cell line in the process taught by Sugimoto. (AM-ITC 00941192 ("Unlike the glycoprotein product of the subject claims, which results from the expression of an exogenous DNA sequence in a non-human eucaryotic host cell, Sugimoto et al. relates to erythropoietin assertedly produced by a human lymphoblastoid cell line.")). Once again, Amgen did not disclose the earlier rejection by Examiner Tanenholtz concerning the obviousness of the process described in the pending claims and claimed in the '179 application.

In the subsequent Amendment dated January 10, 1990 (AM-ITC 00941212-20), applicant cancelled claims 67-75, replacing them with new product-by-process claims 76-83, representing that:

> The Applicant has cancelled claims 67-75 without prejudice. These claims will be the subject of a continuation application. The 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*** [claim 2 was held valid in the District Court decision referred to herein]. The Examiners [Kushan and Schain] have indicated during the interview of December 20, 1989, that these new claims would he entered and be allowable.

(AM-ITC 00941213).

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).

DATED: April 2, 2007

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CERTIFICATE OF SERVICE

I hereby certify that a copy of DEFENDANTS' RESPONSES AND OBJECTIONS TO PLAINTIFF AMGEN INC.'S THIRD SET OF INTERROGATORIES TO DEFENDANTS (NO. 26) was served upon the attorneys of record for the plaintiff (as listed below) by email on the above date.

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