# EXHIBIT 19

**CONTAINS CONFIDENTIAL MATERIAL**
**PURSUANT TO PROTECTIVE ORDER**

**UNITED STATES DISTRICT COURT**
**DISTRICT OF MASSACHUSETTS**

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| AMGEN INC.,<br><br>Plaintiff,<br><br>v.<br><br>F. HOFFMANN-LA ROCHE LTD, a Swiss Company, ROCHE DIAGNOSTICS GmbH, a German Company and HOFFMANN-LA ROCHE INC., a New Jersey Corporation,<br><br>Defendants. | Civil Action No.: 05-12237 WGY |

**APRIL 6, 2007 EXPERT REPORT OF MICHAEL SOFOCLEOUS**

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

## I. Background

*Education and Experience*

1. I am an expert in the field of patent practice and procedure. In particular, I have thirty-eight years of experience with the practices and procedures of the United States Patent and Trademark Office ("PTO" or "Patent Office") and related litigation. My experience includes examining, counseling and interferences.

2. I received my Bachelor of Science degree in Chemistry from Renssalaer Polytechnic Institute in 1965, which was followed by my Juris Doctorate degree in 1973 from The National Law Center at George Washington University.

3. I have been actively involved in the practice of patent law since 1966, with a three year break for military service. Before I began my career in the practice of patent law, I was a food chemist at General Foods Corp. from 1965 to 1966.

4. Prior to entering law school, I began working as a patent examiner at the PTO in 1966. My principal duties included the examination of patent applications in Class 117 (now known as Class 427) (Coating Processes), primarily in the area of electrophotography including processes and related apparatus.

5. In 1974, I was promoted to Primary Examiner, a position which I held until 1975.

6. In 1975, I was promoted to Patent Interference Examiner, a position at the Board of Patent Interferences and in 1976 I became an acting member of the Board of Patent Interferences. As a Patent Interference Examiner (Interlocutory), I was responsible for managing over 1000 interferences from date of declaration until the final hearing, and authored countless interlocutory board decisions and approximately 20 final decisions on priority which constituted final agency actions.

7. In 1985, I was promoted to Administrative Patent Judge (Examiner-in-Chief) of the Board of Patent Appeals and Interferences, a position which I held until 1999. On the Interference side of the Board, I managed an annual docket of approximately 50 to 60 interferences from date of declaration until the final hearing, authored countless decisions on preliminary motions and interlocutory matters, participated in approximately 300 three-member final hearing panels and authored approximately 100 final decisions on priority and patentability which constituted final agency actions. On the Appeals side of the Board, I reviewed adverse decisions of examiners, participated in approximately 360 panels reviewing adverse decisions of

examiners and authored approximately 120 decisions on appeals from such adverse decisions, which constituted final agency actions.

8. In 1999, I entered private practice as an attorney with the law firm of Greenblum & Bernstein, PLC until 2002. In 2002, I became a partner with the law firm of Roberts, Mlotkowski & Hobbes, PC. In 2004, I started my own practice, the Law Office of Michael Sofocleous, where I practice today.

9. A copy of my *Curriculum Vitae* and a list of my publications is attached as Exhibit A.

*Compensation*

10. I am being compensated at my usual rate of $580 per hour in connection with this proceeding. My compensation is in no way dependent on the opinions I express or on the outcome of the case.

*Prior Testimony*

11. In the past four years, I have testified by deposition in the following proceedings:

- *Apotex, Inc. v. Eon Labs Mfg., Inc.*, Civ. Action No. 01 CV 0482 (E.D.N.Y.)
- *Syntex LLC v. Apotex, Inc.*, Case No. CV-01 2214 MJJ (N.D. Cal.)
- *Eli Lilly & Co. v. Zenith Goldline Pharms.*, Case No. IP 01-0443-C-Y/S (S.D. Ind.)
- *John Mezzalingua Associates, Inc. v. Corning Gilbert, Inc.*, Civ. No. 03-C-0354-S (W.D. Wis.)
- *John Mezzalingua Associates, Inc. v. Arris Int'l, Inc.*, Civ. No. 03-C-0353-C (W.D. Wis.)
- *Sanofi-Synthelabo v. Apotex, Inc.*, Civ. Nos. 02-CV-2233 and 02-CV-3672 (S.D.N.Y.)
- *Ortho-McNeil Pharm., Inc v. Kali Labs., Inc.*, Civ. No. 02-5707 (D.N.J.)

- *ICU Medical, Inc. v. B. Braun Medical, Inc.*, Civ. No. 01-3202 CRB (N.D. Cal.)
- *Teva Pharms. v. Pfizer, Inc.*, Civ. Nos. 03cv7423 and 04cv4979 (S.D.N.Y.)
- *Ariad Pharms., Inc. v. Eli Lilly & Co.*, Civ. No. 02 CV 11280 (D. Mass.)
- *Bavarian Nordic, A/S v. Acambis, PLC*, ITC Inv. No. 336-TA-550
- *Innogenetics, N.V. v. Abbott Labs.*, Civ. No. 05-C-0575-C (W.D. Wis.)
- *Omega Patents LLC v. Fortin Auto Radio, Inc.*, Case No. 6:05-CV-01113-ORL-22-DAB (M.D. Fla.)
- *Honeywell Int'l, Inc. v. United States*, Case No. 02-1909C (Fed. Cl.)
- *SmithKline Beecham, PLC v. Teva Pharms. USA*, Civ. Nos. 03-4037, 03-4179, 04-215 and 05-536 (D.N.J.)

12. In the past four years, I have testified at trial as an expert in the following proceedings:

- *Syntex LLC v. Apotex, Inc.*, Case No. CV-01 2214 MJJ (N.D. Cal.)
- *Eli Lilly & Co. v. Zenith Goldline Pharms.*, Case No. IP 01-0443-C-Y/S (S.D. Ind.)
- *ICU Medical, Inc. v. B. Braun Medical, Inc.*, Civ. No. 01-3202 CRB (N.D. Cal.)
- *Bavarian Nordic, A/S v. Acambis, PLC*, ITC Inv. No. 336-TA-550
- *Omega Patents LLC v. Fortin Auto Radio, Inc.*, Case No. 6:05-CV-01113-ORL-22-DAB (M.D. Fla.)
- *Sanofi-Synthelabo v. Apotex, Inc.*, Civ. Nos. 02-CV-2233 and 02-CV-3672 (S.D.N.Y.)

## II. Materials Considered

13. In forming my opinions and preparing this report, I have considered the materials cited and listed in this report, as well as the materials listed in Exhibit B. I have also relied on my many years of experience at the United States Patent and Trademark Office as an examiner and Administrative Patent Law Judge. I have also considered the expert reports of Charles G.

Zaroulis, Ph.D., John Lowe, M.D., Rodney E. Kellems, Ph.D, Bruce Spinowitz, M.D. and Carolyn Bertozzi, Ph.D.

## III. Subject Matter About Which I Expect to Testify

14. I understand that this is a patent infringement action instituted by Amgen for infringement of United States Patent Nos. 5,411,868 ("the '868 patent"), 5,547,933 ("the '933 patent"), 5,618,698 ("the '698 patent"), 5,621,080 ("the '080 patent), 5,756,349 ("the '349 patent") and 5,955,422 ("the '422 patent"). I understand that each of the patents-in-suit shares a common specification with, and claims priority to, U.S. 4,703,008 ("the '008 patent") which expired in 2004.[*] The '008 patent issued from a string of four continuation-in-part applications, with the earliest application filed on December 13, 1983. I understand that the continuation-in-part applications filed on February 21, 1984, September 28, 1984 and November 30, 1984 all added new information to the common specification.

15. I presently plan to testify and give opinions concerning:

(a) Patent Office Procedure and Practice

(b) The Prosecution of the Patents-In-Suit and Related Applications

(c) The Duty of Candor and Good Faith Owed to the Patent Office and Its Examiners and The Duty To Disclose Material Information

(d) Information That Would Have Been Important to a Reasonable Examiner In Allowing the Claims of the Patents-in-Suit

(e) Double Patenting and Violations in Maintaining Consonance

16. Upon consideration of the testimony of (1) the named inventor Lin, (2) other scientists at Amgen, (3) Amgen's in-house counsel and outside patent attorneys, and (4) other

[*] To avoid confusion, when citing within my report to information set forth in the common specification, I generally cite to the '868 patent rather than each patent.

individuals, for example Dr. Goldwasser, as well as my consideration of the file histories of the patents-in-suit and related applications and other relevant material, I am of the opinion that the facts demonstrate that applicants omitted and misrepresented information that would have been important to a reasonable examiner. Applicants, likewise, misdirected the Examiner(s) away from important information and, in many instances, buried important information so that the Examiner would not consider the information.

17. The pattern of conduct in prosecuting the patents-in-suit demonstrates an intentional scheme to obtain patent claims that should not have issued. In my opinion, the file histories show multiple pending applications, with overlapping subject matter being examined by multiple Examiners who were inundated with paper submitted by Applicant and interviews requested by Applicant. Instead of being forthright with the Examiners, Amgen and its prosecuting attorneys did not highlight the most relevant information, thus taking advantage of Patent Office procedures.

18. I note that I am not an expert in the scientific and technical subject matter which forms the basis of the patents-in-suit. To the extent that I offer opinions relating to scientific or technical matters, I am relying on the opinions of other experts, as noted herein.

19. I may address other matters in response to reports or other evidence offered by Amgen. I reserve the right to supplement or amend my opinions in response to opinions expressed by plaintiff's experts, or in light of any additional evidence, testimony, discovery or other information relating to the aforementioned issues that may be provided to me after the date of this report. I expressly reserve the right to supplement or amend my opinions as final

transcripts of relevant testimony become available.* In addition, I expect that I may be asked to consider and testify about issues that may be raised by defendant's experts in their reports or at trial. I reserve the right to rely on any documents that Amgen's experts use. In connection with my testimony, I may use certain graphic or demonstrative exhibits listed herein or attached hereto as Exhibit C, and perhaps those that have not yet been prepared, but which are based on documents identified in this report, to illustrate my opinions.

## IV. PTO Practice and Procedure

### A. The Patent Grant

20. A patent is a document issued by the United States Patent and Trademark Office which provides the owner the right to exclude others from practicing the invention defined by the patent for a specified period of time. Depending on when the application was filed, that statutory term for monopoly terminates after either 17 years from issuance or 20 years from the earliest priority date. (MPEP §2701 (8th ed. Rev. 5, Aug. 2006)).†

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* I understand that the end of fact discovery was April 2, 2007. In some instances the deposition transcripts that I have reviewed are "rough" transcripts and I reserve the right to review and opine regarding any final transcripts and errata which I may be provided.

† "MPEP" refers to the Manual of Patent Examining Procedures. The MPEP provides examiners, applicants, attorneys and agents a reference work on the practices and procedures relating to prosecution of patent applications before the PTO. The MPEP is a regularly used reference for prosecuting agents and attorneys.

Within my report I generally cite to the most current edition of the MPEP and other representative editions as support. From 1983 through 1999 -- during the pendency of the various patents-in-suit -- there have been more than 20 editions/revisions to the MPEP. I note that the substance of the sections to which I refer were in force during the examination of the applications that led to the patents-in-suit and are applicable to the opinions set forth in this report. I expressly reserve the right to cite to rely on the various editions of the MPEP relevant to an action by the PTO or applicant.

264. The '080 patent will expire on August 20, 2013, concurrent with the '933 patent, but nearly 9 years after the '008 patent expired.

## VI. Violations of the Duty of Disclosure, Candor and Good Faith

265. As discussed above, the patent application process before the PTO is an *ex parte* process, not an adversarial process. Moreover, patent examiners have only limited time available to examine a specific application. Given the nature of the patent application process, the integrity of the Patent Office's determinations and the quality of issuing patents are largely dependent upon the honesty, accuracy and completeness of information provided by applicants. Therefore, Patent Office regulations and judicial decisions impose a duty of candor and good faith on applicants including a duty to disclose material information to the examiners. (MPEP §2001 (5th ed. Rev. 3, May 1986); MPEP §2001 (8th ed. Rev. 5, Aug. 2006); *see also* MPEP §2010.02 (5th ed. Rev. 3, May 1986) ("Because of the nature of the relationship between the applicant and the Office, and the nature of the patent grant, applicants and other involved with the preparation and prosecution of the application have a fiduciary relationship and duty toward the Office.")).

266. The applicants' duty of candor and good faith has existed for many decades. (MPEP §2001 (5th ed. Rev. 3, May 1986) ("'the highest degree of candor and good faith' is required of all those participating in the proceedings before the Office")). The duty applies to inventors, prosecuting attorneys and any other individual or employee substantively involved in prosecution of a patent application. (MPEP §2001 (5th ed. Rev. 3, May 1986); MPEP §2001.01 (8th ed. Rev. 5, Aug. 2006); *see also* MPEP§ 2010.02 (5th ed. Rev. 3, May 1986) ("Such individuals are held to exercising a high degree of 'candor and good faith' in their dealings with the Office.")). The obligation of candor, good faith and disclosure of material information

known to the applicant extends throughout the entire life of the patent application, *i.e.* from the moment an application is filed until the day the patent issues.

267. The duty of disclosure is set forth in 37 CFR 1.56 ("Rule 56"). On December 13, 1983, when the first Lin application was filed, Rule 56(a) stated that "information is material where there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent." (MPEP §2001 (5th ed. Rev. 3, May 1986) (citing 37 CFR 1.56)).

268. On March 16, 1992, Rule 56 was amended to read:

> (b) Under this section, information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and
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> (1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or
>
> (2) It refutes, or is inconsistent with, a position the applicant takes in:
>
> (i) Opposing an argument of unpatentability relied on by the Office, or
>
> (ii) Asserting an argument of patentability.
>
> A *prima facie* case of unpatentability is established when the information compels a conclusion that a claim is unpatentable under the preponderance of evidence, burden-of-proof standard, giving each term in the claim its broadest reasonable construction consistent with the specification, and before any consideration is given to evidence which may be submitted in an attempt to establish a contrary conclusion of patentability.

(MPEP §2001.05 (8th ed. Rev. 5, Aug. 2006)). The rule was also amended "to emphasize that there is a duty of candor and good faith which is broader than the duty to disclose material information." (MPEP §2001.04 (5th ed. Rev. 14, 1992)).

269. The 1992 rule change did not supplant the earlier "reasonable examiner standard", but instead provided an additional definition of material information. The Federal Circuit has held that both measures of materiality must be met, and that the "reasonable examiner" standard

is broader and encompasses more information that may be material. It is also noted that a "reasonable examiner" may find a misstatement or omission material even if it would not have rendered the invention unpatentable.

270. It is also recognized that cumulative information is not material, however, whether information is cumulative is a factual determination based on the particular circumstances that may warrant disclosure.

271. During prosecution of the patents-in-suit, the MPEP provided that all important information must be in writing to be considered by the examiner. The Patent Office procedures explicitly state that: "It is clear that the 'disclosures ... to the Office under 37 CFR 1.56 must be in writing as prescribed by 37 CFR 1.2". (MPEP §2002.02 (5th ed. Rev. 3, May 1986)).

272. The MPEP also sets forth specific examples of information that should be disclosed. For example, the rules make clear that an applicant "has the duty to bring to the attention of the examiner ... involved with the examination of a particular application, information within their knowledge as to other co-pending United States applications which are "material to the examination" of the application in question. The applicant cannot assume that the examiner is aware of all information. (MPEP §2001.06(b) (5th ed. Rev. 3, May 1986); MPEP §2001.01 (8th ed. Rev. 5, Aug. 2006); *see also* MPEP §2004 (5th ed. Rev. 3, May 1986) ("it is desirable to be particularly careful that prior art or other information in one application is cited to the examiner in other applications to which it would be material.")). Likewise the MPEP warns that "non-identification of an especially relevant passage buried in an otherwise less or non-relevant text could result in a holding of 'violation of duty of disclosure'". (MPEP §2002.03(b) (5th ed. Rev. 3, May 1986)). The Patent Office encourages applicants to avoid "the submission of long lists of documents", but "if a long list is submitted, highlight those documents which

have specifically been brought to the applicant's attention and/or are known to be of most significance." (MPEP §2004 (5th ed. Rev. 3, May 1986); MPEP §2004 (8th ed. Rev. 5, Aug. 2006)). Also, the Patent Office encourages applicants to provide "a concise explanation of why [the reference was] being submitted and how it is understood to be relevant. Concise explanations are helpful to the Office, particularly where ... a large number of documents are submitted and applicant is aware that one or more are highly relevant to patentability." (MPEP §609A(3) (5th ed., Aug. 1993)).

273. A violation of duty of disclosure with respect to any claim in an application or patent, renders all the claims thereof unpatentable or unenforceable. (MPEP §2016 (5th ed. Rev. 3, May 1986); MPEP §2016 (8th ed. Rev. 5, Aug. 2006)).

274. I understand that the following people had substantive involvement in the prosecution of one or more of the patents-in-suit: Dr. Joan Egrie (11/9/99 Egrie Depo Tr. 176-79); Dr. Thomas Strickland (3/9/07 Strickland Depo Tr. 373); Dr. Fu Kuen Lin (6/21/88 Lin Depo Tr. 432-434); Mr. Michael Borun (3/2/07 Borun Depo Tr. 14-15; 5/17/88 Borun Depo Tr. 25); Mr. Steven Odre (4/2/07 Odre Depo Tr. R. 13-14; 2/14/00 Odre Depo Tr. 15; 7/20/01 First Witness Statement of Steven Michael Odre (UK), ¶2); and Mr. Stuart Watt (3/27/07 Watt Depo Tr. 30; 9/7/00 Watt Trial Tr. 3012).

**A. Omissions to Secure Claims to Extend Amgen's Monopoly**

275. As discussed above, the Lin '008 patent issued on October 27, 1987 and expired on October 27, 2004, seventeen years after it issued. In the course of prosecuting the '179 application, Applicant faced a double patenting rejection of pending claims 70 and 72-75 on the grounds that these process claims were not patentably distinct from claims 1-6 of the '008 patent in view of Yokota *et al*. Examiner Hodges noted that "[a]lthough the conflicting claims are not identical, they 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 for the DNA encoding GM-CSF" in Yokota. ('179 File History, Paper 41, 8/11/94 Office Action at 2). To overcome these rejections, Applicant made several misrepresentations and omissions that resulted in an extension of the life of the '008 patent beyond its 2004 expiration.

### 1. Misrepresentations Regarding *Amgen v. ITC*

276. In Applicant's Amendment and Remarks Under 37 C.F.R. §§1.111 and 1.115 filed on October 7, 1994, Mr. Borun discussed proceedings before the ITC and the subsequent appeal to the Federal Circuit in *Amgen, Inc. v. U.S. Int'l Trade Comm'n*, 902 F.2d 1532 (Fed. Cir. 1990). Commenting on the Federal Circuit's decision, Mr. Borun stated: "There has thus been a judicial determination that rights in the subject matter of the '008 patent claims do not extent to the subject matter of the process claims herein…." ('179 File History, Paper 43, 10/7/94 Amendment at 7).

277. Upon considering the Federal Circuit's decision, I note that the court considered only whether composition claims fell within the ambit of 19 U.S.C. §1337 such that a patentee could rightfully bring an action against a foreign company that allegedly infringed a patented process abroad. 902 F.2d at 1537. The court held that the product claims of the '008 patent could not be used in an action under §1337 because they were not directed to a process. Notably, there was no judicial determination that the '008 product claims were patentably distinct from the processes claimed in the '179 application. This is not surprising because as discussed in Sections V and VII, Mr. Borun had voluntarily cancelled the process claims pending in the application that led to the '008 patent.

### 2. Misrepresentations Regarding the *Fritsch v. Lin* Interferences

278. In the same October 7, 1994 Amendment, Mr. Borun also argued to Examiner Martinell that the declaration of the separate '096 and '097 Interferences highlighted the patentable distinction between product and process claims. Specifically, Mr. Borun stated that "[i]n proceedings before the Board of Patent Appeals and Interferences, separate interferences were drawn for the DNA-related subject matter of [the '008 patent] and the production process subject matter claimed herein." ('179 File History, Paper 43, 10/7/94 Amendment at 7). He concluded that "[i]t 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." ('179 File History, Paper 43, 10/7/94 Amendment at 7). Upon considering the decisions of the Board, I have come across no such conclusion to support Mr. Borun's argument. The declaration of two interferences was merely an administrative matter at the time that the *Fritsch v. Lin* interferences were declared. An examiner could not have an interference declared with an issued patent and an application owned by the same party without a terminal disclaimer. Thus, where a party had an issued patent and a pending application claiming different subject matter, two interferences would have been declared, as was the case here.

279. Mr. Borun failed to inform Examiner Martinell that Applicant took the contradictory position during the '097 Interference proceedings. Particularly, Applicant argued:

> 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, and the litigation was directed to the purified and isolated DNA sequence and host cells transfected or transformed thereby, it is evident that these are only different manifestations of the same invention as acknowledged by Fritsch et al in their Motion Q here …. Stated otherwise, the process language of the Lin patent claims at issue in the litigation ("encoding human EPO") is, for all intents and purposes, a description of the present count.

(Interference No. 102,097, Brief for the Senior Party Lin at 25-26) (emphasis added). I also note that Mr. Borun, Mr. Scott and Amgen's Mr. Odre all appear as "Of Counsel" on the cover page of this filing. (Interference No. 102,097, Brief for the Senior Party Lin at cover).

280. On a related note, Applicant also argued in the '097 Interference that the resolution of priority questions in the '096 Interference necessarily resolved questions of priority with respect to process claims. Applicant stated and emphasized that "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, he is of necessity the first to invent the process of making rEPO using such the host cell." (Interference No. 102,097, 1/25/90 Lin Reply to Fritsch Motion to Terminate Interference at 3) (emphasis in original). In discussing the District Court case, Applicant further stated and emphasized "[t]he 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" the '097 Interference. (Interference No. 102,097, 1/25/90 Lin Reply to Fritsch Motion to Terminate Interference at 9) (emphasis in original).

281. It is my understanding that Mr. Borun and Amgen now assert that the above-noted arguments from the '097 Interference are not admissions by Applicant, but rather recitations of Fritsch's arguments. (*See* 3/2/07 Borun Dep. Tr. at 160-64, 173-78, 180-87, 190-91, 194-202, 271-74). To the extent that this is credited, then Applicant failed to apprise the Board of its true position during the '097 Interference and allowed the Board to decide priority over Fritsch based on a faulty predicate. The Board clearly noted that it relied upon Lin's arguments that an inventor does not need to "be personally involved in carrying out process steps" "where implementation does not require the exercise of inventive skill," such as the expression of the

EPO gene in mammalian host cells and isolation of the resultant glycoprotein. (*Fritsch v. Lin*, 21 U.S.P.Q.2d 1737, 1739 (Bd. Pat. App. & Interf. 1992)). The Board also noted that "[w]e agree with Lin" that 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.*).

282. If the Board misunderstood Lin's argument, Applicant had a duty to correct that misunderstanding, and the failure to do so materially tainted the decision in Interference No. 102,097. (MPEP § 2001.05 (5th ed. Rev. 3, May 1986) ("the duty of disclosure applies in the same manner in less common instances where the official making a decision on a patent application is someone other than the examiner, e.g., a member of the Board of Patent Appeals and Interferences. This is implicit in the duty 'of candor and good faith' toward the 'Office' that is specified" by Rule 56.)). If Lin had in fact believed that the expression of the EPO gene in mammalian host cells and isolation of the resultant glycoprotein conferred patentability, that necessarily would have been important information to the Board of Appeals in deciding priority between Lin and Fritsch.

### 3. Applicant's Failure to Disclose Arguments Made in Opposition Proceedings in Europe

283. I further note that Applicant failed to disclose inconsistent arguments set forth during opposition proceedings in Europe involving Genetics Institute's EP 411 678 ("'678") and EP 209 539 ("'539") patents that would have been important to a reasonable examiner. Applicant argued that "the particular type of glycosylation linkages was simply a result of the type of host cell used to produce the recombinant erythropoietin," acknowledging that the process claims and resultant biologically active erythropoietin were merely an obvious result of

expressing the DNA sequence in a host cell. (*See* EP 411 678 Opposition Proceedings, 10/8/92 Statement of Grounds submitted by Amgen).

#### 4. Mr. Borun Mislead the Examiner Regarding Obviousness-Type Double Patenting Rejections

284. In the October 7, 1994 Amendment submitted in the '179 application, Mr. Borun also materially misstated the proper legal standards to be applied with respect to double patenting analysis. As noted, the Examiner rejected the pending claims of the '179 application as obvious over the '008 patent in view of Yokota *et al*. Mr. Borun argued in the Amendment that "as noted in the decisional authorities, [obviousness-type 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." ('179 File History, Paper 43, 10/7/94 Amendment at 10). While Mr. Borun did not provide "decisional authorities" for this proposition, I note that §804 of the Manual of Patent Examining Procedure allows consideration of the prior art in an obviousness-type double patenting analysis ("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].").

285. I also note that when a double patenting rejection was issued over the Lai '016 patent, Mr. Borun, in a January 3, 1994 Amendment, argued that *In re Braat*, 937 F.2d 589 (Fed. Cir. 1991) mandated the use of a two-way non-obviousness test (discussed below) to determine double patenting. ('179 File History, Paper 33, 1/3/94 Amendment at 7-8). When faced with the double-patenting rejection over the '008 patent, however, Mr. Borun cited *Braat* once again but did not explain to the Examiner that the two-way test did not apply with respect to the '008 patent. ('179 File History, Paper 43, 10/7/94 Amendment at 4-6).

### 5. Mr. Borun's Representations Resulted In Allowance of All Pending Claims and Continued Prosecution of Related Applications

286. Following Mr. Borun's representations regarding prior litigations, the relationship between the claims of the '008 patent and the '179 application and the applicable legal standards, Examiner Martinell issued a Notice of Allowability on all pending claims which, in my opinion, evidences that he was persuaded by Mr. Borun's assertions. ('179 File History, Paper 46, 2/6/95 Notice of Allowability).

287. Furthermore, I note that the '179 application was the parent to those applications resulting in the '698, '422 and '349 patents. As such, Mr. Borun's misrepresentations materially affected the issuance of these later patents which, but for Mr. Borun's misrepresentations, would have likely been rejected for double patenting over the '008 patent.

288. Finally, Applicant's arguments that the products claimed in the pending '178 application were merely the inherent product of the processes claimed in the '179 application suggests that the patents issuing from the '178 line of applications were also tainted by Mr. Borun's representations. In particular, Applicant argued that "if Lin was the first to invent the DNA encoding erythropoietin, and the use of that DNA in a host cell to produce recombinant erythropoietin, then clearly he was the first to invent a recombinant erythropoietin product produced using such a host cell." ('178 File History, Paper 19, 1/10/90 Amendment at 6). Applicant also argued that new claims in the '178 application "parallel claim 2 of U.S. Patent No. 4,703,008." ('178 File History, Paper 19, 1/10/90 Amendment at 5).

### 6. Applicant's Knowledge of the Delayed Process Claims

289. As discussed in Sections V and VII, the Patent Office placed the process claims in the same restricted group as the claims that issued as the '008 patent indicating that they were not separate and distinct inventions. Mr. Borun then voluntarily withdrew the process claims and

placed them in a continuing application on October 23, 1987, three months after receiving Notice of Allowability in the '298 application that issued as the '008 patent. ('298 File History, Paper 22, 7/13/87 Notice of Allowability). Because the patent term at the time was 17 years from the issuance of the patent, he knew or should have known that the '179 continuation application with the process claims would issue later than the '008 patent, thereby extending Lin's monopoly.

### B. Misconduct to Overcome the Lai Double-Patenting Rejection

#### 1. Information Regarding Delay Would Have Been Important to a Reasonable Examiner

290. During prosecution of the '179 application, Examiner Hodges issued a September 1, 1993 Office Action, rejecting pending claims 65-69 as being "directed to an invention not patentably distinct from claim 9 of commonly assigned Patent No. 4,667,016 (Lai et al.)." ('179 File History, Paper 29, 9/1/93 Office Action at 6).

291. To overcome the rejection, Mr. Borun applied a two-way non-obviousness test (as discussed in Section VII) and argued that "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." ('179 File History, Paper 33, 1/3/94 Amendment and Response at 12). He further stated that the "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." (*Id.*). Likewise, Mr. Borun represented that "issuance of the pending claims in the present ['179] application would provide no extension whenever of the protection of the Lai et al., much less an unjustified extension thereof." (*Id.* at 9).

292. Responding to Applicant's comments, Examiner Hodges apparently 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 of 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.

('179 File History, Paper 34, 2/15/94 Office Action at 2 (emphasis added)). Examiner Hodges never reinstated his obviousness-type double patenting rejection in light of the Lai '016 patent.

293. However, as discussed in detail below in Section VII, Mr. Borun expressly and voluntarily withdrew the pending process claims from the '298 application, which issued as the '008 patent. ('298 File History, Paper 15, 3/11/87 Amendment and Reply at 27). The "interference in its immediate parent, 06/675,298" actually was an interference of the issued '008 patent, not the '298 application as Examiner Hodges apparently believed. Had the process claims not been withdrawn, they would have either (1) been part of that interference rather than in a separate patent altogether or (2) in an issued patent. Moreover, Applicant did not file the '179 application -- a continuation of Ser. No. 675,298 -- until after the issuance of the Lai '016 patent. 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.

294. Despite Examiner Hodges' factual mistakes and oversights regarding the process claims at issue in the '179 Application, Mr. Borun did not correct the facts underlying Examiner Hodges' analysis. This information would have been important to a reasonable examiner, especially in light of Examiner Hodges' conclusion that "the instantly claimed method *is* an

obvious variation of the process of Lai et al." ('179 File History, Paper 34, 2/15/94 Office Action at 2 (emphasis in original))

**2. Applicant's Knowledge of the Delayed Process Claims**

295. Mr. Borun, who had intimate involvement with the prosecution of all the patents-in-suit and the underlying '008 patent, (*see* 3/2/07 Borun Dep. Tr. at 14-15), had every reason not to correct Examiner Hodges factual errors. Had the Examiner been given the correct information, the double-patenting rejection would have been sustained given Examiner Hodges conclusion that "the instantly claimed method *is* an obvious variation of the process of Lai et al." Thus, he knew that pointing out the correct facts underlying the delay in the process claims would affect patentability of the claims. Instead, because of Mr. Borun's omission of important facts and failure to correct the record, Amgen has enjoyed the right to exclude the public from purifying recombinant EPO from mammalian cell culture as claimed by the Lai '016 method since 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 2004 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.

**C. Misrepresentations Regarding the State of the Prior Art**

**1. Information Regarding the State of the Prior Art Would Have Been Important to a Reasonable Examiner**

296. I have considered the expert reports of John Lowe, M.D. and Rodney E. Kellems, Ph.D regarding the state of the art with respect to recominant processes for expressing proteins and glycoproteins

297. During the prosecution of Ser. No. 113,179 (which led to the '868 and '698 patents-in-suit), 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.

('179 File History, Paper 3, Declaration Accompanying Petition to Make Special at 6 (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. ('179 File History, Paper 3, Declaration Accompanying Petition to Make Special to Ser. No. 675,298).

298. As discussed in Section V, 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 was approved and there is no indication that the special status of the '179 File History was ever revoked.

299. Following approval of the Petition ('179 File History, Paper 8, 5/24/88 Applicant's Second Preliminary Amendment), Mr. Borun misrepresented the state of the art regarding recombinant production of what Amgen termed 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 ('179 File History, Paper 8, 5/24/88 Applicant's Second Preliminary Amendment at 6, 20; Paper 14, 9/27/88 Applicant's Reply at 5). For example Mr. Borun stated 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.

('179 File History, Paper 8, 5/24/88 Applicant's Second Preliminary Amendment at 12).

300. Then pending Claim 65 related "to a novel series of process steps wherein a mammalian host cell capable of glycosylating the expressed polypeptides is first transformed or transfected with a DNA sequence . . . .." ('179 File History, Paper 8, 5/24/88 Applicant's Second Preliminary Amendment at 6; *see also* Paper 14, 9/27/88 Applicant's Reply at 5; *see also* '868 patent claims). In arguing patentability, Mr. Borun stated 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." ('179 File History, Paper 8, 5/24/88 Applicant's Second Preliminary Amendment at 10).

301. Applicants relied on this distinction throughout the prosecution of the '868 patent claims to overcome prior art rejections. (*See, e.g.*, '179 File History, Paper 10, 9/14/88 ("Odre urges that EPO is an obligate glycoprotein and that the Yokota et al. multi CSF is not an obligate protein...."); Paper 14, 9/27/88 Applicant's Reply at 5 ("it appears that Applicant may have been the first to have successfully produced a human obligate glycoprotein by recombinant methods"); Paper 33, 1/3/94 Applicant's Amendment at 11 ("As previously maintained by the Applicant, his production of 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 glycosylation for in vivo biological activity. Lai et al. claim 9 is silent on the issue of glycosylation and in vivo biological activity."); Paper 43, 10/7/94 Applicant's Amendment at 9-10 ("To the extent that Yokota et al. might have been cited as prior art 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.")).

**a. Misrepresentations Regarding tPA**

302. Mr. Borun acknowledged tissue plasminogen activator (tPA) as an "obligate" human glycoprotein. ('179 File History, Paper 8, 5/24/88 Applicant's Second Preliminary Amendment at 17 ("Naturally occurring tPA is believed by applicant to share with erythropoietin the characteristic of being an obligate human glycoprotein.")).

303. Before a first Office Action was issued, Mr. Borun submitted a Second Preliminary Amendment "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. ('179 File History, Paper 8, 5/24/88 Applicant's Second Preliminary Amendment at 15; 3/2/07 Borun Depo. Tr. 212-213). 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." ('179 File History, Paper 8, 5/24/88 Applicant's Second Preliminary Amendment at 16-17). 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." (*Id.* at 17).

304. 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." ('179 File History, Paper 8, 5/24/88 Applicant's Second Preliminary Amendment at 18). He argued that three applications located were not relevant to patentability of Ser. No. 113,179.

305. In particular, Mr. Borun cited EP 0 093 619 ("EP '619") and included accurate applicant, publication and priority information (*Id.*; 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).

('179 File History, Paper 8, 5/24/88 Applicant's Second Preliminary Amendment at 18).

306. 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).

307. By 1984 -- four years before Mr. Borun submitted the Preliminary Amendment - public press releases showed that animal testing demonstrated 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).

308. 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 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.

309. Amgen also did not disclose the related counterpart patent, 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. Therefore, the U.S. counterpart application would not have been cumulative. Instead, Mr. Borun disclosed German language references DE 33 48 289 and DE 33 48 289 (without translation) relating to production of tPA. ('179 File History, Paper 43, 10/7/94 Applicant's Amendment at 9; Paper 44, IDS and PTO-1449).

310. In the Second Preliminary Amendment which disclosed Mr. Borun's search results for the Petition to Make Special, he 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. ('179 File History, Paper 8, 5/24/88 Second Preliminary Amendment at 18; Paper 43, 10/7/94 Applicant's Amendment at 9). 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"('179 File History, Paper 8, 5/24/88 Second Preliminary Amendment at 18-19) and, in my opinion, a reasonable examiner would not an undertake an extensive independent evaluation given the apparent thoroughness of Mr. Borun's search and his sworn statement that he was familiar with the pertinent prior art and what it disclosed.

311. In addition, during the '179 prosecution, no steps were taken to correct Mr. Borun's misrepresentations regarding the state of art regarding tPA and "obligate" glycoproteins. Instead, in a September 27, 1988 Reply, Mr. Odre represented that:

> 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.

('179 File History, Paper 44, 9/27/88 Applicant's Reply at 5) (emphasis added). Given (1) the November 9, 1983 publication date of EP '619, (2) the April 7, 1983 filing date (and May 5, 1982 priority date) of counterpart patent U.S. 4,766,075 which was not disclosed, and (3) the interferon art discussed below which was not disclosed, this statement was a continuing misrepresentation of the state of the art regarding "obligate" human glycoproteins. Subsequent to this Reply, Examiner Tanenholtz issued a Notice of Allowability for pending process claims 65-69. ('179 File History, Paper 17, Notice of Allowability).

312. 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 ('179 File History, Paper 32, 1/3/94 Information Disclosure Statement and IDS), 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" (*Id.* at 1-2), insinuating to the new examiner -- Examiner Hodges -- that the reference had been substantively considered and overcome in proving patentability of the pending process claims. In my opinion, as stated above, any review of these references would have been cursory, and each page of the 25-page PTO-1449 Form indicates that the Examiner considered the references on the same day.

313. Mr. Borun and Amgen also relied upon his earlier misrepresentation regarding EP '619 to argue patentability with respect to a double-patenting rejection. 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 EP '619 reference was already considered by the previous examiners. ('179 File History, Paper 43, 10/7/94 Applicant's Amendment at 8 ("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)" and "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."); *Id.* at 10 ("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. ('179 File History, Paper 46, 2/6/95 Notice of Allowability).

**b. Non-Disclosure of Interferon Art**

314. 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)).

315. 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).

316. The file history makes plain that, until Amgen persuaded the Examiner of its purported distinction of "obligate" glycoproteins and the state of the art, 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. ('179 File History, Paper 39, 8/3/88 Office Action at 2 (citing Yokota U.S. 4,695,542 disclosing production of GM-CSF); Paper 14, 9/27/88 Applicant's Reply at 4 (characterizing Yokota as disclosing multi-CSF or IL-3 (interleukin-3)); Paper 43, 10/7/94 Applicant's Amendment at 3). Given the Examiner's rejections of the process claims based on other recombinant processes, in my opinion, information regarding tPA and interferon would have been important to the reasonable examiner, especially in light of its attempt to distinguish "obligate" glycoproteins from other recombinant glycoproteins.

**2. Facts Regarding Applicant's Knowledge of the Art**

317. The '179 file history shows that Mr. Borun, Mr. Watt and Mr. Odre were aware of and tracking patents and publications relating to these other human proteins. (*e.g.,* '179 File History, Paper 8, 5/24/88 Second Preliminary Amendment at 16-17 ("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."); Paper 32, PTO-1449 at 2 (U.S. 4,757,006 disclosing human factor VIII:C); Paper 44, PTO-1449 at 2 (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); Taniguchi *et al*., "Structure and expression of a cloned cDNA for human interleukin-2," Nature, 285:628-34 (1983)).

318. These attorneys were clearly aware that Genentech was involved in work with tPA and had numerous public press releases at the same time the '179 application was being examined. Likewise, they were aware that Cetus Corp. was researching recombinant interferon as indicated by submission of the McCormick references. Moreover, both Genentech and Cetus Corporation were competitors in the biotechnology field, and Amgen undertook competitive intelligence and monitoring in relation to its competitors. (*See* 11/6/97 Watt Depo Tr. 9-13; 5/24/89 Rathmann Depo Tr. 60). Additionally, the file histories indicate that some references were submitted to the Patent Office even if they were published after the last CIP '298 parent application was filed. (*See, e.g.*, 1/3/94 PTO-1449 form, reference C96 (1991), reference C95 (1990), references C1, C9, C15 and C18 (1986), reference C54 (1985), etc…).

319. The argument that there are "obligate" glycoprotein, as opposed to other types of glycoproteins, was introduced in the '179 application only after Applicant received a prior art rejection in the '298 application over recombinant processes. ('298 File History, Paper 12, 10/2/86 Applicant's Amendment and Reply at 4). Given the Examiner's repeated rejections over prior art recombinant processes to produce glycoproteins, and Applicant's tactic in trying to distinguish between different types of glycoproteins to argue patentability, Messrs. Borun, Odre and Watt had every reason to mislead the Examiner regarding the state of the art and references regarding glycoproteins. The tPA and interferon references discussed above would have bolstered the Examiner's rejections and made securing process claims that much more difficult.

### D. Affirmative Misrepresentations and Omissions Regarding Molecular Weight

#### 1. Information Regarding Apparent Molecular Weight Would Have Been Important to a Reasonable Examiner

320. I have considered the expert report of Carolyn Bertozzi, Ph.D. in connection with glycosylation and molecular weight. On December 20, 1995, during prosecution of the applications that led to the '933 patent, Mr. Borun added a new file claim 101 which issued as claim 2. ('774 File History, Paper 50, 12/20/95). Claim 2 reads: "The non-naturally occurring EPO glycoprotein product according to claim 1 wherein said product has a higher molecular weight than human urinary EPO as measured by SDS-PAGE." (*Id.* at 2; '933 patent, claim 2). The claim was allowed without any patentability rejection.

321. I understand that the common specification of the Lin patents states that: "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." ('868 patent, col. 5:67-6:7). I also understand that Miyake *et al*., "Purification of Human Erythropoietin", J. Biol. Chem., 252(15): 5558-64 (1977) found that human erythropoietin had an apparent molecular weight by SDS-PAGE of 34,000 daltons (asialo form) or 39,000 daltons (native form). I further understand that Dr. Egrie 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).

322. Documents in Amgen's possession show that recombinant erythropoietin made in accordance with the Lin disclosure does not have a "higher molecular weight on SDS-PAGE" than human urinary EPO. This information was not submitted to Examiner Martinell in examining file claim 101 and would have been important to patentability under §112. In my

opinion, if this information had been properly disclosed, the claim would not have issued. This is confirmed by the fact that the claim has been held invalid as indefinite, not enabled, and due to an insufficient written description. *Amgen v. TKT*, 126 F. Supp. 2d 69, 154-56, 164-65.

323. Documents show that the prosecuting attorneys knew or should have known that the claim they were prosecuting was not patentable under §112. For example, Amgen's Product License Agreement, which was not submitted to the Examiner, shows that Amgen's rEPO does not have a higher molecular weight than urinary EPO. (AM-ITC 00092870; AM-ITC 00092880). Amgen told the FDA that "determinations based on gel filtration under nondenaturing conditions or gel electrophoresis in the presence of SDS are not reliable ...". (AM-ITC 00092870).

324. Additionally, the following documents expressly state that the apparent molecular weight of recombinant EPO is not higher than that of human urinary EPO:

- AM-ITC01072474-501 at 494: "Recombinant ... human EPO produced by COS cells have the same molecular weight as native urinary EPO (Goldwasser's 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 ..." (*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 ...."

- 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 ..."

- 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. ... 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).

- Egrie *et al*., 1986, Characterization and Biological Effects of Recombinant Human Erythropoietin, *Immunobiol*., vol. 172, pp. 213-224 (1986): "As seen in Figure 4, purified rHuEPO migrates identically with an apparent molecular weight of approximately 36,000 daltons ...."

- Vapnek *et al*., "Comparative Studies of Natural and Recombinant Erythropoietin," *Banbury Reports 29:Therapeutic Peptides and Proteins*, 241-56 (1988): "As shown in Figure 3, both rh-Epo and urinary Epo have an apparent molecular weight of approximately 36,000."

325. Similarly, various declarations submitted in foreign offices also contain important information showing that recombinant erythropoietin does not have a higher molecular weight than urinary EPO. Dr. Strickland 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 Amgen apparently never submitted this information or declaration to the U.S. Examiner(s).

326. 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 apparently was not submitted to the U.S. patent Examiners.

327. 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. In that document, assigned to Mr. Odre, 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).

328. None of these documents, articles or declarations were submitted to the Examiner in an IDS as directed by the MPEP. None are listed on the face of the patents as a "Reference Cited" or on an IDS as a "reference of record". Mr. Borun filed an IDS after the '334 Interference, which 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 record" from European Opposition Proceedings regarding the foreign counterpart EP 0148 605. The Egrie articles are not included as being a "reference of record." (*See* discussion in Section V; *compare* AM-ITC 00941422-449 (submitting 2 boxes of documents purportedly including exhibits from *Amgen v. Chugai* (but not the Egrie file)) *with* TKT Trial Tr. at 2863:9-2864:4 (Mr. Borun's testimony that the Egrie file was an exhibit in that action)).

329. Furthermore, these references are not cumulative to one another: the references are from different time periods, show that Amgen widely disseminated this information to those of skill in the art in different publications and presentation, and some references relate to COS EPO while other relate to CHO EPO. In particular, representations to other patent agencies would be important and are not cumulative.

330. I understand that Amgen argues that at least the "Egrie Input Data" and Egrie *et al*., 1986, "Characterization and Biological Effects of Recombinant Human Erythropoietin", *Immunobiol.*, vol. 172, pp. 213-224 (1986) were submitted to the Board of Appeals during the '334 Interference. Although these may have been exhibits, there is no specific mention of these documents in the Board's Final Decision. Furthermore, for the reasons discussed in Section IV and VI, this is not proper disclosure under the duty of candor and good faith. Moreover, the count in the '334 Interference did not focus on or consider the patentability of the limitation "a higher molecular weight than human urinary EPO as measured by SDS-PAGE", and the Examiner's indicated review of the interference file was 2 years before the claim was even added to the application. I also note that the '334 Interference file states that the decision was noted and nothing more. (AM-ITC 00950983-AM-ITC 00950991 at AM-ITC 00950991).

**2. Applicant's Knowledge of Apparent Molecular Weight**

331. I understand that Dr. Egrie was intimately involved with the prosecution of the patents-in-suit. (11/9/99 Egrie Depo Tr. 176-79). 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 that recombinant erythropoietin did not have a higher apparent molecular

weight that human urinary EPO. Indeed, as shown above, she plainly and unequivocally concluded that recombinant erythropoietin has the same molecular weight as native urinary EPO

332. 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 (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) he acknowledges that he 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). Furthermore 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), normally reviews information that he has requested (2/5/2002 Borun Trial Tr. 248:22-249:18) and has indicated 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). Moreover, Dr. Lin declared under oath in a submission to the PTO that the 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).

333. Documents show that 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). 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 (*e.g.* AM-ITC 00312455-73)

and declarations provided by Amgen employees. (*e.g.* AM-ITC 00312260-71; AM-ITC 00312441-45).

334. Additionally, with respect to the articles and presentations, Amgen had a policy in place to review and approve dissemination of research information. (*See* 3/29/07 Watt Depo Tr. 135-38).

335. Likewise, although it is unclear what method was used to determine the molecular weight, 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). This measurement is clearly lower than the value reported for urinary erythropoietin by Lin in his common specification.

### E. Affirmative Misrepresentations and Omissions Regarding COS rEPO

#### 1. Information Regarding Glycosylation of COS rEPO Would Have Been Important to a Reasonable Examiner

##### a. The Prosecution History

336. I have considered the expert report of Carolyn Bertozzi, Ph.D. in connection with glycosylation. In addition to the conduct discussed above, in order to obtain product claims to erythropoietin (which I understand is a naturally occurring hormone) and to overcome patentability rejections, Amgen submitted claims, including:

- "having glycosylation which differs from that of human urinary erythropoietin" (*e.g.*, '933 patent; '874 File History, Paper 37, 6/13/94 Preliminary Amendment; '874 File History, Paper 42, 2/16/95 Amendment and Request for Reconsideration at 4; '774 File History, Paper 50, 12/20/95 Second Preliminary Amendment and Remarks at 2).

- "has glycosylation which differs from that of human urinary erythropoietin" (*e.g.* '080 patent; '556 File History, Paper 4, Claims for Discussion; '556 File History, Paper 6, Third Preliminary Amendment at 7) and

- "having an average carbohydrate composition which differs from that of naturally occurring [human] erythropoietin." (*e.g.* '933 patent; '178 File History, Paper 1, Application at 101; '178 File History, Paper 6, Amendment and Reply at 3; '178 File History, Paper 11, Amendment at 1; '178 File History, Paper 15, Amendment at 1; '178 File History, Paper 18, Examiner Interview Summary Record at 2, '178 File History, Paper 19, Amendment at 1; '774 File History, Paper 50, Second Preliminary Amendment at 3).

337. During prosecution, applicant maintained that the claimed inventions covered recombinant erythropoietin expressed in a variety of host cells including both CHO and COS cells. (*e.g.* '178 File History, Paper 6, Amendment and Reply at 6; '774 File History, Paper 50, Second Preliminary Amendment at 5; *see also* '179 File History, Paper 33, 1/3/94 Amendment and Response at 5 ("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; '178 File History, Paper 6, Amendment and Reply at 4; '178 File History, Paper 11, Amendment at 2; '178 File History, Paper 18, Examiner Interview Summary Record at 2; '178 File History, Paper 19, Amendment at 2; '874 File History, Paper 37, Preliminary Amendment at 2; '874 File History, Paper 42, Amendment and Request for Reconsideration at 4), "wherein the host cell is a COS cell" ('178 File History, Paper 6, Amendment and Reply at 4; '178 File History, Paper 11, Amendment at 2) and "wherein the host cell is a CHO cell." ('933 patent, '178 File History, Paper 6, Amendment and Reply at 4; '178 File History, Paper 11, Amendment at 2; '178 File History, Paper 18, Examiner Interview Summary Record at 2; '178 File History, Paper 19, Amendment at 2; '874 File History, Paper 37, Preliminary Amendment at 2; '874 File History, Paper 42, Amendment and Request for Reconsideration at 4; '774 File History, Paper 50, Second Preliminary Amendment at 3). 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." ('178 File History, Paper 6, Amendment and Reply at 6). Accordingly, to support and prove patentability of the independent claims with limitations to glycosylation and average carbohydrate composition, differences between human EPO and recombinant EPO from COS and CHO cells needed to be shown.

338. 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.

('178 File History, Paper 4, 6/2/88 Office Action at 6-7 (emphasis added)).

339. 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.

('178 File History, Paper 6, Amendment and Reply at 6 (emphasis added)).

340. Furthermore, Mr. Sharp stated that:

> 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.

('178 File History, Paper 6, Amendment and Reply at 9-10 (emphasis added)).

341. In arguing for patentability in the light of 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.

('178 File History, Paper 6, Amendment and Reply at 11-12 (emphasis added); *see also* 11/23/99 Borun Depo. Tr. 125-126).

342. Rather than submit information comparing the glycosylation and average carbohydrate composition of human urinary EPO versus recombinant EPO expressed in COS

cells, the Strickland Declaration disclosed information pertaining only to the comparison of human urinary EPO versus recombinant EPO expressed in CHO cells. ('178 File History, Paper 7, Strickland Declaration at 2 ("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.")).

343. 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. <u>This analysis indicates that recombinant erythropoietin as described by Serial No. 113,178 has a different carbohydrate composition than naturally occurring urinary erythropoietin</u>.

(AM-ITC 00941134 (emphasis added)).

344. However, the recombinant erythropoietin as described by Ser. No. 113,178 includes COS r-EPO, which Amgen knew had not shown patentable differences in glycosylation and average carbohydrate composition. The Strickland Declaration omitted this information and focused solely on supposed differences between CHO r-EPO and human urinary EPO.

345. As a consequence of the information chosen to be disclosed by the Strickland Declaration and that which was withheld, Examiner Kushan concluded 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.

('178 File History, Paper 9, 2/10/89 Office Action at 4-5). In order to overcome the §103 prior art rejection, however, Amgen submitted arguments relating to commercial success, long-felt need and other secondary considerations. ('178 File History, Paper 9, 5/24/89 Examiner Interview Summary Record; '178 File History, Paper 11, Amendment at 5-8; '178 File History, Paper 13, 6/20/89 Office Action at 7).

346. Even though Examiner Kushan withdrew his §102 rejection, Mr. Byrne 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)" ('178 File History, Paper 11, Amendment at 4) and continued to omit material information regarding COS rEPO covered by the pending claims. ('178 File History, Paper 11, Amendment at 1-2; '178 File History, Paper 13, 6/20/89 Office Action at 4 ("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 in vivo activity when administered to humans.")).

347. 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 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.

('178 File History, Paper 13, 6/20/89 Office Action at 5-6 (emphasis added)).

348. Applicant did not submit any information regarding COS rEPO to the Examiner, and opted to rely on the Strickland Declaration to overcome a different 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.

('178 File History, Paper 15, Amendment at 5 (emphasis added)). In response, Examiner Kushan dropped his rejection.

349. An Examiner Interview Summary Record indicates 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." ('874 File History, Paper 39, 9/7/94 Examiner Interview Summary Record (emphasis added)). This apparently refers to "the January, 1994 expert statement of Dr. Richard Cummings ... as submitted in proceedings before the European Patent Office in counterpart European Patent EP 0 148 605" ('874 File History, 2/16/95 Amendment and attached Cummings Declaration), 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.

350. Like the Strickland declaration, the Cummings declaration focuses primarily on CHO rEPO. The only mention of COS rEPO (Declaration of Cummings in Appeal Proceedings Against EP 148 607 at ¶ 6.2) is in passing and relies on information lifted directly from the Lin application which, as discussed below, ignores test results set forth by Dr. Egrie's internal work

at Amgen and articles touting the "similarities" in glycosylation. Dr. Cummings did not include any published literature regarding COS rEPO but directed the Examiner's focus 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", 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. ('874 File History, 2/16/95 Amendment and attached Cummings Declaration). Moreover, it is unclear whether the Egrie articles referenced by Dr. Cummings related to CHO rEPO or COS rEPO. Based on the file histories I have considered, it appears that 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.

351. To the extent that Dr. Cummings discussed the "2 articles by Egrie", he misrepresented the conclusions presented by the authors of those references. Although it is not clear from the submission to the PTO which of the Egrie articles Dr. Cummings referred to, as discussed below, each Egrie article regarding COS rEPO concluded that it and human urinary EPO "migrate identically." But, he and Mr. Borun did not disclose those conclusions.

352. 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." ('874 File History, Paper 42, Amendment and Request for Reconsideration at 8-9). It is my understanding that the Takeuchi article, however, relates to CHO rEPO, not COS rEPO. (Takeuchi *et al.,* "Comparative Study of Asparagine-linked Sugar Chains of Human Erythropoietins Purified from Urine and the Culture Medium of Recombinant Chinese Hamster Ovary Cells").

353. When prosecution resumed after the termination of Interference 102,334, Examiner Fitzgerald allowed pending claims 76-83 ('178 File History, Paper 33, 11/22/93 Examiner Interview Summary Record; '178 File History, Paper 34, 12/29/93 Office Action at 3), 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." ('774 File History, Paper 45, Preliminary Amendment at 2; '774 File History, Paper 50, 12/20/95 Second Preliminary Amendment at 4). However, claim 99 did not have text identical to either claim 76 or the sole Count, broadening the claim from "which differs from that of naturally occurring human erythropoietin" to "which differs from that of naturally occurring erythropoietin."

354. 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")). In my opinion, it appears that Amgen exploited those rules advantageously. The Examiner allowed those claims, as well as dependent claims, to issue without further rejection. ('774 File History, Paper 52, Notice of Allowability).

### b. References Relevant to COS rEPO

355. At least the following information discloses 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 (emphasis added)).

- 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." (emphasis added)

- 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." (emphasis added)

- 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 (emphasis added)). (*See also* AM-ITC 00557617-23).

356. Similarly, the internal file given to Mr. Borun shows that Dr. Egrie 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).

357. I understand that Amgen has argued that these documents are not completely inconsistent with the information submitted to the Patent Office and, therefore, did not need to be submitted. However, this is information that Amgen and its scientists were disseminating to the public which state that tests suggest that recombinant EPO is glycosylated to the same extent as urinary EPO. Based on the rejections lodged against these claims, this information, in my opinion, would have been important to a reasonable examiner for determining the patentability of "differences" in glycosylation and average carbohydrate composition.

358. Furthermore, the various articles and presentations are not cumulative to one another for the reasons I discussed above in regards to average molecular weight. In addition, because Amgen decided to argue for patentability by submitting multiple articles to suggest differences in glycosylation and, thus, tipping the scales in its favor based on sheer volume of evidence, the multiple articles discussing the similarities in glycosylation should have been submitted as well. Without Applicant submitting all articles noting a similarity in glycosylation or notifying the Examiner of the existence of these articles, the Examiner would not have known the extent of the dissemination of that information and, in my opinion, would be left with the misimpression that the evidence of a similarity was an anomaly.

**c. The '334 Interference**

359. To the extent that Amgen relies on the '334 Interference file to show that material information was submitted to the PTO, as discussed above, a reasonable examiner would not

know that statements regarding the similarities of glycosylation existed. The '334 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. Therefore, any alleged statement regarding COS rEPO in the interference file does not qualify as proper disclosure to the examiner.

360. 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 U.S.P.Q.2d 1739, 1742 (Bd. Pat. App. & Interf. 1991); Interference No. 102,334, Brief for Senior Party Lin at 47 ("The Fritsch et al motion is based on Section 102(b), not 103.")). 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.

361. For example, the Declaration of Fu-Kuen Lin (AM-ITC 00295809-295816) states:

> 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 00295811 (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 00295812 (emphasis added)).

* * *

> 8. .... 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 in vivo 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 00295814 (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 00295815 (emphasis added)).

362. The Declaration of Thomas W. Strickland (AM-ITC 00339454-64), filed in conjunction with the '334 Interference, makes clear that the declaration he filed in the '178 application, discussed above, concerned CHO-rEPO that:

> 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 00339456 (emphasis added)).

363. The Declaration of Jeffrey K Browne (AM-ITC 00361603-00361627) also focuses on CHO r-EPO:

> (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 00361603 (emphasis added).

364. The Brief for Senior Party Lin, which lists both Mr. Borun and Mr. Odre as counsel, also focuses on recombinant erythropoietin expressed in CHO cells, for example:

> - 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 00832911 (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 00832913 (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 00832914-15 (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 00832918 (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 00832919 (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). (AM-ITC 00832920 (emphasis added)).

365. The Final Decision from the Board of Patent Appeals and Interferences makes plain that the Board -- like the Examiner -- focused on CHO rEPO and not COS rEPO. (*Fritsch v. Lin*, 21 U.S.P.Q.2d 1739 (Bd. Pat. App. & Interf. 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, as discussed, the Final Decision makes no mention of any Egrie articles or other reference regarding COS rEPO. Furthermore, the Board stated that it did not determine patentability under §103.

**2. Facts Regarding Applicant's Knowledge of COS rEPO**

366. For the reasons discussed above regarding average molecular weight, the attorneys and scientists involved in prosecuting the '933 and '080 patents were aware of the references discussing the similarity in glycosylation and carbohydrate composition of COS cells. In my opinion, they knew or should have known the references would have been important to a reasonable examiner, especially given the rejections which stated any differences did not rise to a patentable distinction. It is also 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. In my opinion, 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, he knew or should have known that the omitted and misrepresented information would have been important because he argued that the remaining claims also covered rEPO expressed by COS cells (*e.g.* '933 patent; '080 patent) and at the time

the patents were prosecuted, it is my understanding that only COS and CHO cells had been used by Lin. Therefore, not only would this information raise §103 issues, but §112 issues as well.

### F. Affirmative Misrepresentations and Omissions Regarding CHO rEPO

#### 1. Information Regarding Glycosylation of CHO rEPO Would Have Been Important to a Reasonable Examiner

367. I have considered the expert report of Carolyn Bertozzi, Ph.D. in connection with glycosylation. In addition to the information outlined above, Amgen also withheld and misrepresented information regarding CHO rEPO. Applicant's attorneys, Messrs. Borun and Odre, affirmatively told the Examiner 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." ('774 File History, Paper 39). 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, Mr. Borun offered the Cummings Declaration as discussed above.

368. Dr. Egrie's data includes statements that there were no differences when Lin's CHO rEPO was compared to Lot 82 and Alpha Therapeutics urinary EPO. This data was not provided in either (1) the Cummings declaration or (2) any filings submitted by the applicants in response to office actions. (AM-ITC 01072481; AM-ITC 01072486 (both showing "CHO(2) + Lot 82 same size", "α Therapeutics - is same size as CHO + Lot 82"). Amgen apparently relied 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. 298-299, 300-301).

369. Furthermore, the Cummings declaration that Mr. Borun submitted to support patentability did not disclose important information. As discussed above in relation to COS rEPO, Cummings mentioned two articles by Egrie *et al.* but he did not give any information to identify 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." (emphasis added)

- 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." (emphasis added)

370. 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. As previously discussed, Amgen filed IDS statements and said they were submitting "all references of record."

371. Dr. Cumming's citation to Browne, "Erythropoietin: Gene Cloning, Protein Structure, and Biological Properties," *Cold Spring Harbor Symposium* (1986), regarding CHO rEPO appears to be a passing reference with respect to an 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 he did not include the Browne article, in my opinion, implying that the Browne article was not relevant to the main point of his declaration.

372. Mr. Borun did not submit the Browne reference in the IDS which included "references of record" in the prosecution ('874 File History, Paper 36, 4/8/94 IDS) 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 U.S.P.Q.2d 1739, 1742 (Bd. Pat. App. & Interf. 1991)).

373. Similarly, Amgen and its attorneys did not disclose Vapnek *et al.*, "Comparative Studies of Natural and Recombinant Erythropoietin," *Banbury Reports 2*9*: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 to the Examiner. The article also reports that experiments "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."

374. 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).

375. Furthermore, after Applicant 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. And even after the error became apparent, Mr. Borun and Amgen's attorneys left the erroneous information in the specification even though the information could have been removed from later applications (through a CIP application) without losing the earlier filing dates.

376. In February 1992, during the prosecution of the '933 patent, Dr. Strickland submitted a declaration (AM-ITC 00326183-98) opposing EP 0 411 678, a European patent application which has the same disclosure as WO 86/03520 (3/9/07 Strickland Depo. Tr. 275-277) which was submitted among 394 references to the examiner. ('874 File History, Paper 36, 4/8/91 IDS and PTO-1449). In his 1992 declaration, Dr. Strickland addressed 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 and Dr. Strickland's earlier declaration submitted to the Examiner did not discuss the impact of experimental and analytical error in conducting tests to determine differences or similarities in glycosylation and average carbohydrate composition. I note that the Patent Office does not have facilities to run experimental testing. This type of information regarding experimental error

would have been important to a reasonable examiner in determining whether any reported differences between recombinant erythropoietin and human urinary erythropoietin were significant enough to support patentability.

#### 2. Facts Regarding Applicant's Knowledge of the CHO rEPO

377. For the reasons discussed above regarding average molecular weight and the glycosylation of COS rEPO, the attorneys and scientists involved in prosecuting the '933 and '080 patents were aware of the references discussing the similarity in glycosylation and carbohydrate composition of recombinant erythropoietin from CHO cells. Those individuals knew or should have known that the information would have been important to a reasonable examiner. Likewise, my opinion regarding why information submitted during the '334 Interference was not properly disclosed to the Examiner in compliance with duty of good faith and candor is equally applicable.

### G. Concealing the Standard Used in RIA From the '349 Examiner

#### 1. Information Regarding the EPO Standard Would Have Been Important to a Reasonable Examiner

378. I have considered the expert report of Dr. Charles G. Zaroulis setting forth reasons why the standard used in radioimmunoassay is important. I understand that every claim of the '349 patent includes a limitation to a 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). I also understand that Example 2 of the common specification sets forth part of the protocol for conducting the radioimmunoassay. ('868 patent, col. 17:30-68). I note, however, the protocol discloses only "an erythropoietin standard" and not the standard used by Dr. Lin and his

colleagues in developing his "invention" as discussed below. (*Compare* '349 patent, col. 16:39-4 *with* AM-ITC 00551000; 3/27/07 Egrie Depo. Tr. 194-195)).

379. I also understand that Example 10 of the common specification further sets forth experimental results using RIA to determine "effective production rates" as "U of erythropoietin per $10^6$ cells in 48 hours" ('868 patent, col. 28:5-25)), but also does not disclose what standard the inventor used to conduct the RIA in support of his claims.

380. Documents and testimony shows that different urinary erythropoietin was available for use (3/27/07 Egrie Depo. Tr. R. 160-163, 169-170, 184; AM-ITC 00061675; AM-ITC 00550986; AM-ITC00551040), and that 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). For example, Dr. Egrie testified that she 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.")).

381. Documents also show that, as of September 1984, before the last CIP application was filed upon which 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 and, as I understand, unavailable to the public because it was an internal Kirin-Amgen creation.

382. Documents also show that Applicant's units ("U") are arbitrary units which do not equate to international units ("IU") (AM-ITC 00558618; 3/27/07 Egrie Depo. Tr. 191-192),

which I understand are accepted units by those of skill in the art. 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.*). Applicant never disclosed this information to the Examiner.

383. This information would have been important to the reasonable examiner. As explained by Dr. Zaroulis, this information is important to the patentability of the claims under §112 (definiteness and enablement). Moreover, because the claims require "growth in excess of [x] U of erythropoietin per $10^6$ cells in 48 hours as determined by radioimmunoassay", 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. (MPEP §2004 ($5^{th}$ ed. Rev. 3, May 1986), MPEP §2004 ($8^{th}$ ed. Rev. 5, Aug. 2006) ("Make sure that the best mode is described.")). Likewise, because Dr. Egrie was intimately involved in developing and conducting the RIA assays disclosed in the patent and required to meet a claim limitation, the question of proper inventorship would have been important to the Examiner in determining patentability of the claims. (MPEP §2004 ($5^{th}$ ed. Rev. 3, May 1986), MPEP §2004 ($8^{th}$ ed. Rev. 5, Aug. 2006) ("If the are questions [about proper inventorship], call them to the attention of the Patent and Trademark Office.")).

384. From my consideration of the file histories, however, it appears that none of the information set forth above was disclosed to Examiner Martinell, the Examiner who issued the '349 patent. Nonetheless, Applicant pressed ahead causing issuance of the '349 patent claims.

**2. Applicant's Knowledge of the EPO Standard**

385. Dr. Egrie admits that she developed the radioimmunoassay used to evaluate recombinant erythropoietin and that her RIA methodology is disclosed in the common specification. (3/27/07 Egrie Depo. Tr. 106-107). Dr. Lin relied on the RIA protocol and associated test results as support for the claim limitations of the '349 patent and the written description. (3/28/07 Lin Depo. Tr. 162-163). Mr. Borun has testified that he spoke to Dr. Egrie in conjunction with preparing and prosecuting the patents (*see* 11/23/99 Borun Depo Tr. 23-24), and the record shows that Drs. Egrie and Lin continued their involvement during the prosecution of the patents-in-suit and were in regular contact with the prosecuting attorney. Dr. Lin and Dr. Egrie submitted various declarations and have testified on behalf of Amgen during the continuing prosecution.

386. Documents cited above show that Dr. Egrie and Dr. Lin were aware that the standard EPO they used was unavailable before the '298 application was filed, and that the units disclosed were not defined. Dr. Egrie and Mr. Borun knew, or at a minimum should have known, that the information would have been important in determining whether the claims are enabled, definite and complied with the best mode requirement as well as in determining whether Lin was correctly named as the sole inventor.

### H. Non-Disclosure of Amgen Work With the 1411 Cell Line

#### 1. The 1411 Cell Line Would Have Been Important to a Reasonable Examiner

387. 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.

388. Examiner Tanenholtz 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).

389. 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.

('298 File History, Paper 20, 7/10/87 Applicant's Amendment at 20 (emphasis added)). In response to Mr. Borun's statements, Examiner Tanenholtz allowed all the pending claims to issue. ('298 File History, Paper 21, 7/30/87 Examiner Interview Summary).

390. Applicant and Mr. Borun, however, failed to disclose that "cells producing high levels" of erythropoietin were available and that supernatant from such cells was being tested at

Amgen. 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).

391. 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 Erythropoietin (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 erythropoiesis 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).

392. Moreover, published literature (which apparently was not disclosed to the examiner) related to the cells plainly supported the Examiner's 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.")).

393. Given Mr. Borun's representation regarding erythropoietin producing cell lines in responding to a prior art rejection, the reasonable examiner would have found the 1411 cells important in determining patentability.

**2. Applicant's Knowledge of the 1411 Cell Line**

394. Dr. Lin and Amgen have admitted that they were looking for cells that expressed human erythropoietin. (3/28/07 Lin Depo. Tr. 19-22, 32). At the same time Lin's colleague, Dr. Egrie who worked closely with Lin on the recombinant EPO project, was aware of the 1411 cell line and was running RIA assays on the cell line. (3/27/07 Egrie Depo Tr. 277-280). Likewise, Dr. Goldwasser, who was a consultant to Amgen and Dr. Lin on the project, was also aware of the EPO-producing cells.

395. Given Examiner Tanenholtz's prior art rejections, submitting information regarding the 1411 cells would have strengthened the Examiner's argument against patentability of the pending claims. Final rejection of the claims then pending in the '298 application would have made arguing patentability in subsequent applications (*i.e.* the patents-in-suit) much more difficult if not impossible. Accordingly, there was every incentive to omit information regarding the 1411 cells.

## I. Amgen's Prosecution of Claims Rejected by Different Examiners

### 1. Information Regarding the Rejections in Related Applications Would Have Been Important to a Reasonable Examiner

396. As discussed in Section V, the patents-in-suit issued from two co-pending lines of applications: Ser. No. 113,178 (" the '178 application") and Ser. No. 113,179 (" the '179 application"). Both of these applications were filed on the same day, October 23, 1987. (*See* '178 File History, Paper 1; '179 File History, Paper 1). The '178 line of applications include the '080 and '933 issued patents, while the '179 line of applications include the '868, '698, '422 and '349 line of applications.

397. I have considered the expert report of Drs. John Lowe and Rodney E. Kellems, Ph.D, explaining the similarity of the claims of the various patents-in-suit, in the context of obviousness-type double patenting and obviousness over the prior art. I have also considered the certified file histories of the patents-in-suit for rejections made in the co-pending lines of applications. It is my opinion that advocating for the patentability of a claim in one application that is substantially similar to a previously rejected claim in another application, both applications being examined by different examiners during the same time period, would have been important to a reasonable examiner because another examiner has taken the position that the claim is unpatentable.

#### a. August 3, 1988 Office Action in the '179 Application

398. On May 24, 1988, Mr. Borun filed a Second Preliminary Amendment adding 5 new claims (65-69) to the '179 application. New claim 65 recited:

> A process for the preparation of an <u>in vivo</u> biologically active glycosylated polypeptide comprising the steps of :
>
> (a) growing a mammalian host 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 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.

Claims 66-69 further limited this independent claim in terms of host cell expression of cDNA (claim 68) or genomic DNA (claim 69) sequences, particularly in a CHO cell (claim 66) or COS cell (claim 67). (*See* '179 File History, Paper 8, 5/24/88 Amendment).

399. In an August 3, 1988 Office Action, Examiner Tanenholtz rejected these claims as obvious and unpatentable over Yokota *et al.*, "who [taught] a process as claimed herein differing only in using a mammalian DNA sequence that encodes a different polypeptide." ('179 File History, Paper 9, 8/3/88 Office Action at 2). Applicant had argued that the claimed invention was different "on the ground of achieving unexpected results, namely producing a glycosylated polypeptide. However, [Tanenholtz noted], Yokoto [sic] et al teach the production and in fact claim the production of a glycosylated product." ('179 File History, Paper 9, 8/3/99 Office Action at 3). Examiner Tanenholtz also noted that Gething *et al.* taught that eukaryotic cells

innately glycosylate proteins. The Examiner concluded that it would therefore be expected that following the Yokota procedure would necessarily result in a product that was glycosylated. (*Id*.).

400. Soon after the rejection of the '179 pending claims, Applicant filed an Amendment and Reply in connection with the co-pending '178 application. In this December 1, 1988 Amendment and Reply, Applicant amended claims 41, 55 and 56, and added new claims 61-66. Claim 41 was amended to be directed to "a 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 dependent claims 61-66 further limited the product as being the product of expression of an exogenous DNA sequence in a eukaryotic host cell (claim 61), where the exogenous DNA sequence is a cDNA sequence (claim 62) or a genomic sequence (claim 63), and where the host cell is a mammalian cell (claim 64), in particular a COS cell (claim 65) or a CHO cell (claim 66). (*See* '178 File History, Paper 6, 12/1/88 Amendment).

401. When Applicant faced a rejection in the '179 Application, Mr. Odre argued that the pending claims 65-69 were directed to

> a novel series of process steps wherein a mammalian host cell capable of glycosylating the expressed polypeptides is first transformed or transfected with a DNA sequence 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).

('179 File History, Paper 14, 9/27/88 Reply at 2). This argument shows that Applicant regarded his invention in the '178 as simply the product of the process claimed in the '179, claims which

were rejected before Applicant's December 1, 1988 amendment. Yet, there is no evidence that Applicant disclosed that prior rejection to the '179 Examiner, and it is clear that Applicant advocated for the patentability of the '178 claims in spite of the prior '179 rejection. It is further noted that the Examiners of the two lines of applications were different. Examiner Tanenholtz issued the rejection in the '179, yet the Examiner responsible for the '178 was Examiner Kushan. (*See* '178 File History, Paper 8, 1/26/89 Examiner Interview (Examiner noted as "Kushan")).

**b. Applicant's Reliance on Product-by-Process Claims and Continued Failure to Apprise Examiner Kushan of the Facts During the '178 Prosecution**

402. On February 10, 1989, Examiner Kushan issued a Final Office Action rejecting the pending claims of the '178 Application over concerns that the particular glycosylation of recombinant erythropoietin and urinary erythropoietin was not sufficiently defined. (*See* '178 File History, Paper 9, 2/10/89 Office Action).

403. To respond to Examiner Kushan's concerns, Applicant cancelled all claims and added new claims 67-75, which were product-by-process claims. The erythropoietin of the claimed invention was newly defined as a "glycoprotein product of the expression of an exogenous DNA sequence in a eukaryotic host cell…." ('178 File History, Paper 11, 6/2/89 Amendment at 3-4). Again, there is no evidence that Applicant informed Examiner Kushan of Examiner Tanenholtz's prior rejection of the '179 process claims over Yokota and Gething, despite transforming its "product" claims into "product-by-process" claims.

404. On July 11, 1989, Applicant filed an amendment to claim 67 to limit the host cell to a "non-human eucaryotic host cell" to avoid a prior art rejection over Sugimoto *et al*., which utilized a human lymphoblastoid cell line. ('178 File History, Paper 15, 7/11/89 Amendment at 5). Once again, there is no evidence that Applicant informed Examiner Kushan of Examiner Tanenholtz's prior rejection of the substantially similar '179 process claims.

405. Applicant's continued failure to disclose is particularly noteworthy in light of its January 10, 1990 Amendment in which Applicant cancelled claims 67-75 and added new claims 76-83 (also product-by-process claims), noting that "[t]hese new claims parallel claim 2 of U.S. Patent No. 4,703,008 (Lin '008 patent), the parent of the instant application," which was held valid by the District Court in *Amgen v. Chugai*. ('178 File History, Paper 19, 1/10/90 Amendment at 5). This confirms that Applicant regarded these applications as parts of the same overall invention.

406. Applicant's continued failure to disclose is also noteworthy in light of arguments it made with respect to suspension of prosecution during the *Fritsch v. Lin* Interferences Nos. 102,096 and 102,097. Applicant argued that the decision in *Amgen, Inc. v. Chugai Pharm. Co. & Genetics Inst., Inc.,* Civ. Action No. 87-2617-Y (D. Mass. Dec. 11, 1989) was fully dispositive of any priority issue in both the '096 and '097 interferences (which dealt with the '008 patent and '179 application, respectively), as well as any priority issue in the subject '178 application. Applicant stated and emphasized: "Therefore, it is submitted that if Lin was the first to invent the DNA encoding erythropoietin, and the use of that DNA in a host cell to produce recombinant erythropoietin, then clearly he was the first to invent a recombinant erythropoietin product produced using such a host cell." (*See* '178 File History, Paper 19, 1/10/90 Amendment at 6) (emphasis in original). Despite Applicant's argument that priority determinations in the two lines of applications should rise and fall together, Applicant did not inform Examiner Kushan of Examiner Tanenholtz's rejection in the co-pending '179 application.

**c. Applicant's Actions in the '874 Continuation Application Prosecution**

407. As noted *supra*, Mr. Borun filed the '874 application as a continuation of the '178 application on February 28, 1994. ('874 File History, Paper 35, 2/28/84 Continuation Application).

408. On April 8, 1994, Mr. Borun filed an Information Disclosure Statement ("IDS") listing 394 references, including references noted as being "of record" from the '178 application and the '179 application, references cited in the 35 U.S.C. § 282 Notice from the *Amgen v. Chugai* District of Massachusetts proceeding as well as admitted exhibits, and references of record from the European Opposition Proceeding regarding EPO 148,605. Among the cited references were Yokota and Gething, both cited as being of record from the '179 application. While these references were disclosed, it is my opinion that they were effectively concealed from Examiner Kushan because their significance was not disclosed, *i.e.* forming the basis of a rejection in the co-pending '179 application. In my experience, an Examiner would have spent approximately 20 hours examining any particular application, and if all of that time had been devoted to examining the references cited in this IDS, that would equate to approximately three minutes reviewing each of the 394 references. Applicant could have provided "a concise explanation of why [the reference was] being submitted and how it is understood to be relevant. Concise explanations are helpful to the Office, particularly where ... a large number of documents are submitted and applicant is aware that one or more are highly relevant to patentability." (MPEP §609A(3) (5th ed., Aug. 1993)). Applicant, in failing to highlight the material nature of these references to the co-pending '179 application, effectively concealed the pertinence of these references. Furthermore, Applicant could have filed a copy of the Office Action from the co-pending '179 application. (*See* '178 File History, Paper 36, 4/8/94 IDS).

409. On June 13, 1994, Applicant filed an amendment canceling all pending claims and adding new claims 84-94 (which were renumbered as claims 87-97). New claim 86 (renumbered to 89) was a product-by-process claim, with the first process step reading "(a) growing … mammalian host cells transformed or transfected with an isolated DNA sequence encoding the human erythropoietin amino acid sequence …." Once again, there is no evidence that Applicant informed the Examiner Martinell of Examiner Tanenholtz's prior rejection of the substantially similar '179 process claims.

**d. Applicant's Continued Omissions in Subsequent Applications**

410. Applicant later filed the '556 application (which led to the '080 patent) and the '774 application (which led to the '933 patent) as continuations of the '874 application. (*See* '774 File History, Paper 44; '556 File History, Paper 1, Application). There is no evidence that Applicant ever apprised the Examiner of the material rejections from the '179 application based on Yokota and Gething which, in my opinion, materially affected the issuance of the '080 and '933 patents.

**2. Rejections in the '178 Application**

**a. June 2, 1988 Office Action in the '178 Application**

411. In a June 2, 1998 Office Action, Examiner Kushan rejected all claims pending in the '178 application, including claim 55. Claim 55 is a dependent claim directed to a pharmaceutical composition comprising an effective amount of polypeptide. Examiner Kushan rejected claim 55 under § 103 as being obvious over Miyake *et al*., Takezawa *et al.*, Chiba *et al*. or Sugimoto *et al*. in view of Papayannopoulo *et al*. The Examiner noted that each of the four cited references "would enable one of ordinary skill in the art to prepare biologically active, homogenous human EPO," and Papayannopoulo taught the effectiveness of EPO in a murine model. ('178 File History, Paper 4, 6/2/88 Office Action at 9). In view of these references, "one

would find it obvious to use EPO in a treatment to restore hemoglobin concentration in vivo." (*Id.*).

412. In a November 6, 1990 Preliminary Amendment filed in connection with the '741 application (a continuation of the '179 application, in the line of applications that led to the '422 patent), Applicant sought to prosecute substantially similar claims to a pharmaceutical composition or preparation containing erythropoietin. (*See* '741 File History, Paper 2, 11/6/90 Preliminary Amendment at 9). Applicant failed to inform Examiner Nolan of the prior rejection of claim 55 of the '178 application issued by Examiner Kushan. Similarly, when subsequent continuation applications were filed on the '741 (*i.e.*, the '073 application and the '197 application, FWC applications leading to the '422 patent), Applicant continued to prosecute these claims without informing Examiner Stanton of the rejection of the claim 55. (*See* '197 File History, Paper 18, 12/20/93 Amendment).

**b. February 10, 1989 Office Action in the '178 Application**

413. In a February 10, 1989 Office Action, Examiner Kushan rejected all pending claims in the '178 application, including claims 55 and 61-66. As was held in the June 2, 1989 Office Action, claims 55 and 61-66 were rejected under § 103 as being obvious over Miyake *et al*., Chiba *et al*., Takezawa *et al*. or Sugimoto *et al*. in view of Papayannapoulo *et al*. Examiner Kushan once again concluded that "[t]he ordinary practioner [sic], having available a species of EPO (rHuEPO) which behaves in vivo in the identical fashion as the naturally occurring species, would find a method of erythropoietin therapy to be no more than a routine extrapolation (if any) from the teachings of Papayannapoulo et al." ('178 File History, Paper 9, 2/10/89 Office Action at 9).

414. Despite Examiner Kushan's rejection, Applicant continued to prosecute substantially similar claims in the '179 line of applications. As noted above, Applicant failed to

inform Examiner Nolan of the prior rejection of claim 55 of the '178 application issued by Examiner Kushan when Mr. Kokulis filed a November 6, 1990 Preliminary Amendment in connection with the '741 application (which ultimately issued as the '422 patent). (*See* '741 File History, Paper 2, 11/6/90 Preliminary Amendment at 9). Similarly, when subsequent continuation applications were filed on the '741 (*i.e.*, the '073 application and the '197 application), Applicant continued to prosecute these claims without informing Examiner Stanton of the rejection of the claim 55. (*See* '197 File History, Paper 18, 12/20/93 Amendment). Finally, in a January 3, 1994 Amendment in the '179 application, Applicant added new claims 72-75 that were substantially similar to rejected claims 62-66, but did not inform Examiner Hodges of Examiner Kushan's rejection. (*See* '179 File History, Paper 33, 1/3/94 Amendment).

**c. June 20 and September 18, 1989 Office Actions in the '178 Application**

415. In a June 20, 1989 Office Action, Examiner Kushan rejected, among others, pending claims 67-73 in the '178 application. Claim 67, the sole independent claim, read:

> A glycoprotein product of the expression of an exogenous DNA sequence in a eukaryotic host cell, said 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 having an average carbohydrate composition which differs from that of naturally occurring human erythropoietin.

('178 File History, Paper 13, 6/20/89 Office Action). Claims 67-73 were rejected under (1) the doctrine of obviousness-type double patenting over the Lai '016 patent, (2) § 102(b) (or alternatively § 103) over Sugimoto *et al*., and (3) § 103 as obvious over Sugimoto *et al*. in view of Papayannopoulo *et al*. Examiner Kushan noted that the Lai '016 taught a procedure for the purification of the recombinant EPO claimed in the instant application and, therefore, a person of ordinary skill would be able to practice the claimed invention from the teachings of the Lai '016.

As to Sugimoto *et al*., Examiner Kushan noted that while Applicant had shown a difference between recombinant EPO and urinary EPO, that difference could not be extrapolated to show a difference between recombinant EPO and lymphoblastoid derived human EPO, as taught by Sugimoto *et al*. Finally, Examiner Kushan rejected the claims as obvious over Sugimoto *et al*. in view of Papayannapoulo *et al*. for the same reasons set forth in the June 2, 1988 and February 10, 1989 Office Actions. (*See* '178 File History, Paper 13, 6/20/89 Office Action).

416. In a September 18, 1989 Final Office Action, Examiner Kushan once again issued a rejection of claims 67-75 under the doctrine of obviousness-type double patenting over the Lai '016 patent.

417. Despite these rejections, Applicant continued to prosecute substantially similar claims in the '179 line of applications (which ultimately led to the '422 patent). In particular, Applicant sought to prosecute pharmaceutical composition claims, the patentability of which would have been questionable in light of the Examiner's rejection over Sugimoto *et al*. in view of Papayannapoulo *et al*. As with the prior Office Actions, Applicant failed to inform Examiner Nolan of the rejection of claims of the '178 application issued by Examiner Kushan. Similarly, when subsequent continuation applications were filed on the '741 (*i.e.*, the '073 application and the '197 application, which ultimately led to the '422 patent), Applicant continued to prosecute these claims without informing Examiner Stanton of the rejection of these claims. (*See* '197 File History, Paper 18, 12/20/93 Amendment). Furthermore, in a January 3, 1994 Amendment in the '179 application, Applicant added new claims 72-75 that were substantially similar to rejected claims 68-72, but did not inform Examiner Hodges of Examiner Kushan's rejection. (*See* '179 File History, Paper 33, 1/3/94 Amendment).

#### 3. Applicant's Knowledge of Relevant Rejections

418. The same attorneys (Messrs. Odre and Borun) had substantial involvement in the prosecution of both lines of applications such that they would have been aware of these inconsistencies. (*See, e.g.*, '178 File History, Paper 3, 10/23/87 Amendment (signed by Mr. Borun); '178 File History, Paper 8, 1/26/89 Examiner Interview (Mr. Odre present); '179 File History, Paper 2, 2/9/88 Associate Power of Attorney (Mr. Borun appointing Mr. Odre as a prosecuting attorney); 3/2/07 Borun Depo Tr. 14-15). Both attorneys were interested in securing issued claims for their client in order to have patents to enforce against third parties such as Genetics Institute, and to maintain and extent the patent monopoly first secured by the '008 patent. Both attorneys were experienced practitioners that knew, or at a minimum should have known, that the rejections in the co-pending related patents would have been important to the reasonable examiner because they could potentially support additional rejections in the applications in which they were not disclosed and either delay issuance or prevent issuance of claims.

### J. Non-Disclosure of the Baron-Goldwasser Clinical Study

#### 1. Information Regarding the Baron-Goldwasser Clinical Study Would Have Been Important to a Reasonable Examiner

419. I have considered the expert report of Bruce Spinowitz, M.D. in connection with human administration and the Baron-Goldwasser clinical study. The '422 patent-in-suit consists of the following claims:

> 1. A pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is purified from mammalian cells grown in culture.
>
> 2. A pharmaceutically-acceptable preparation containing a therapeutically effective amount of erythropoietin wherein human serum albumin is mixed with said erythropoietin.

('422 patent, claims).

420. On June 1, 1994, Examiner Stanton issued an Office Action, rejecting the predecessor file claims 61-63 over the prior art Miyake and Takezawa references, stating that:

> • "Since erythropoietin was known compound with accepted therapeutic use, one of ordinary skill in the art at the time of the instant invention, would have been motivated to prepare pharmaceutical compositions comprising erythropoietin. Further, since HSA was a known and an acceptable pharmaceutical excipient, one would have used HSA in preparing any pharmaceutical composition. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to have prepared the claimed pharmaceutical compositions comprising erythropoietin and HSA excipient, one would have used HSA."
>
> • "It is apparent that the claimed erythropoietin (EPO) compositions read on any erythropoietin molecule regardless of its source. In particular, the specification indicates that glycosylated erythropoietin that exhibits the characteristic amino acid sequence and biological properties of naturally occurring erythropoietin is envisioned. Therefore, 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."

('197 File History, Paper 20, 6/1/94 Office Action at 3-4).

421. Examiner Stanton also noted that a therapeutically "effective" amount was indefinite under §112. ('197 File History, Paper 20, 6/1/94 Office Action at 2).

422. In arguing for patentability, Applicant told the Examiner 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.

('197 File History, Paper 23, 12/1/94 Request for Reconsideration at 2 (emphasis added)).

423. As to the Examiner's §103 rejections, Attorney Scott stated that:

> The Examiner has cited three prior references showing various levels of purification of erythropoietin from urinary sources and combined those with Bock and/or the present specification. First, it should be noted that none of these cited references (except the present specification) disclose or even suggest the claimed compositions. Bock relates to a totally different protein. The Examiner has in hindsight combined references disclosing urinary erythropoietin with references which suggest the use of HSA in general in pharmaceutical. This is improper.

('197 File History, Paper 23, 12/1/94 Request for Reconsideration at 4-5).

424. Two papers by Goldwasser were discussed during an interview on April 21, 1999.

In a subsequent submission, the Applicant explained that:

> With respect to Claim 65, the two Goldwasser references reviewed at the interview disclose the use of bovine serum albumin to stabilize partially purified erythropoietin preparations obtained from sheep plasma. These references do not disclose a pharmaceutically acceptable preparation, and there is no indication that BSA or other stabilizing additive would be necessary once the purified EPO was obtained. In fact, the Chapter 10, Erythropoietin, Goldwasser reference states: "It is obvious that, when further purification or protein determinations are being carried out, exogenous protein cannot be added. Loss of activity can then be minimized by keeping solutions as concentrated and as cold as possible."

('197 File History, Paper 33, 4/28/99 Amendment at 5). Thus, the Applicant argued to the Examiner that the prior art did not disclose or suggest the use of human serum albumin with human erythropoietin.

425. However, Dr. Lin and the attorneys at Amgen were aware that there was a prior art erythropoietin composition that (1) was "therapeutically effective" as disclosed by the patent and argued during examination, and (2) that the prior art erythropoietin composition was comprised of human serum albumin. (*See, e.g.*, 9/7/00 Watt Trial Tr. 2964-66; 6/8/00 Lin Trial Tr. 1095, 1100-03).

426. Lin and his colleagues were aware that in the 1980's Dr. Baron and Dr. Goldwasser -- who I understand was a consultant who worked closely with Amgen on its erythropoietin project -- conducted human clinical trials with urinary erythropoietin ("the Baron-Goldwasser clinical study"). (6/7/00 Lin Trial Tr. 947-48; 6/8/00 Lin Trial Tr. 1095). However, 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. (2/11/00 Watt Depo Tr. 151-163; 2/14/00 Odre Depo Tr. 100-104, 106-07).

427. I understand that Judge Young has already held the Baron-Goldwasser clinical trials to be available as prior art under §§102/103, and this has been affirmed by the Court of Appeals of the Federal Circuit. The information from the Baron-Goldwasser clinical study would have been important to a reasonable examiner because it could have been used as an invalidating reference under §102 and §103 for the reasons explained in the June 1, 1994 Office Action. The Baron-Goldwasser study used a pharmaceutical composition of erythropoietin and human serum albumin. (AM-ITC 00873885-903; AM-ITC00084770-80). In addition, the study

reported that "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).

**2. Applicant's Knowledge of the Baron-Goldwasser Study**

428. Individuals at Amgen, including at least Mr. Watt -- Amgen's in-house counsel -- were intimately involved in prosecuting the '422 patent. (9/7/00 Watt Trial Tr. 2964-66). Mr. Watt even participated in an Examiner Interview that discussed two articles by Dr. Goldwasser which did not disclose the Baron-Goldwasser study. ('197 File History, Paper 32, 4/21/99 Examiner Interview). Accordingly, he would have been aware that work relating to urinary erythropoietin, and the work by Dr. Goldwasser and his colleagues, was important to the Examiner.

429. From the arguments exchanged during examination, Applicant was aware that it 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.")). As discussed above, the Examiner made clear that he would not issue a patent to a composition found in the prior art, including compositions with human serum albumin. Likewise, the PTO repeatedly told Applicant, since the very first application that source limitations alone would not confer patentability on products described in the prior art. ('024 File History, Paper 4, 9/23/85 Office

Action; *see also* '197 File History, Paper 26, 3/31/95 Letter). Thus, there was every reason not to disclose the Baron-Goldwasser clinical study in order to gain an issued patent, and but for Applicant's conduct, the claims of the '422 patent would not have issued.

430. Both documents and testimony I have considered 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). For example, at least Mr. Odre and Drs. Lin, Egrie, Strickland and Browne, were aware that a pharmaceutical composition of erythropoietin and human serum albumin were used in the Baron-Goldwasser study, as well as the patient results. (AM-ITC 00573885-903). At least Drs. Lin, Egrie, Strickland and Browne -- who were involved Amgen's erythropoietin project and in the drafting and prosecution of the patents -- were aware of the Baron-Goldwasser clinical study (and that Applicant used the study "as a guideline" to determine dosing for administering EPO). (AM-ITC 00557514-27). At least Dr. Lin was aware that the Goldwasser-Baron study resulted "a mild to modest increase in reticulocyte number", "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 " an increase in red cell mass following the treatment program." (AM-ITC 00245727-29; *see also* AM-ITC 00084770-80; AM-ITC 00849306-41). All which were indications of a "therapeutically effective amount" as argued to the Patent Office.

431. 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. Furthermore, the final decision in each interference does not refer to the Baron-Goldwasser study.

432. As discussed in Section V, none of the 3 interference counts had to do with pharmaceutical compositions of erythropoietin, let alone with human serum albumin. The '096 Interference related to a "DNA sequence encoding human erythropoietin", the '097 Interference related to a "process for the preparation of an in vivo biologically active glycosylated polypeptide", and the '334 Interference related to a "non-naturally occurring glycoprotein product". Without Applicant specifically 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, Applicant has admitted that it did not disclose the data or clinical protocols even in the context of the interferences. Furthermore, there is no indication that Examiner Stanton reviewed any of the interference files in issuing the '422 patent. (*See* '741, '073 and '197 Search Notes). The Search Notes indicate that the Examiner consulted the claims of the '179 application that led to the '868 patent, but not the related Interference file. Moreover, it is not surprising that Examiner Stanton would not have reviewed the '334 Interference because the '933 patent is not in the same application line as the '422 patent.

433. The IDS statements filed by Applicant 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 Applicant's attorneys discussed prior art erythropoietin

disclosed by Goldwasser during an interview with Examiners Stanton and Martinell ('197 File History, Paper 32, 4/21/99 Examiner Interview Summary Record), the discussion was limited to partially purified erythropoietin preparations obtained from sheep plasma, not the clinical study relating to human urinary EPO. ('197 File History, Paper 33, 4/28/99 Amendment at 5).

## VII. Issues Relating to Obviousness-Type Double Patenting

434. The doctrine of double patenting seeks to prevent the unjustified extension of exclusivity beyond the term of a patent. If an examiner determines that an applicant's claimed invention is identical to ("same invention type double patenting") or obvious in view of subject matter claimed in an issued patent or another pending application ("obvious-type double patenting"), the examiner should issue a double-patenting rejection. (MPEP §804-§804.03 (5th ed. Rev. 8, May 1988); MPEP §804-§804.03 (8th ed. Rev. 6, Aug. 2006)).

435. As discussed above, the Patent Office is required to grant a single patent for a single invention. The purpose of this requirement is to prevent an applicant from extending the right to exclusivity afforded by the patent grant by filing multiple applications (including continuation applications) on the same or similar inventions which issue at different times. Patent Office policy recognizes that the public should be able to act on the assumption that upon expiration of the patent, it will be free to use not only the invention claimed in the patent, but also modifications or variants which would have been obvious to those of ordinary skill in the art at the time the invention was made. The doctrine of obviousness-type double patenting is applied to prevent the issuance of claims that are obvious variations of claims in an earlier patent having a common inventor or owner. (MPEP §804 (5th ed. Rev. 8, May 1988); MPEP §804 (8th ed. Rev. 6, Aug. 2006)).

436. A rejection for double-patenting is available where the application and reference patent (or application) has a common inventor, assignee or owner. A determination of priority is

Dated: April 6, 2007

Michael Sofocleous

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**CERTIFICATE OF SERVICE**

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

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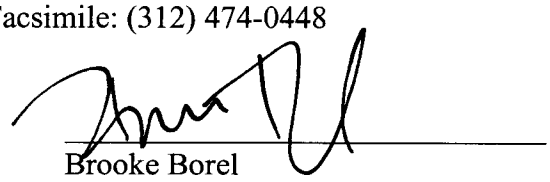

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