Exhibit 2

UNITED STATES DISTRICT COURT

DISTRICT OF MASSACHUSETTS

AMGEN INC., Plaintiff, v. HOECHST MARION ROUSSEL, INC. and TRANSKARYOTIC THERAPIES, INC., Defendants.	Civil Action No. 97-10814-WGY

MEMORANDUM IN SUPPORT OF AMGEN'S MOTION FOR SUMMARY JUDGMENT OF NO INEQUITABLE CONDUCT

TABLE OF CONTENTS

I. Introduction

Entry of summary judgment of no inequitable conduct is proper because Amgen disclosed to the Patent Office ("PTO") the very information alleged by the Defendants to be withheld. Moreover, the information was not simply disclosed, but the prosecution record shows that it was considered by the PTO and the claims were held patentable to Amgen in view of the information. In the face of these disclosures, Defendants' allegations of failure to disclose material information are false, and there can be no inequitable conduct.

In their Amended Answer, filed on January 10, 2000, Defendants specified three acts as providing the basis for their defense of inequitable conduct:

1. the purported failure to cite a 1978 study by Dr. Eugene Goldwasser and colleagues in which urinary EPO was administered to three patients without results;

2. providing supposedly misleading and incorrect information relating to the molecular weight comparisons set out in Example 10 of the patents and withholding a document entitled "Egrie Input"; and

3. the alleged failure to correct the monosaccharide composition data set out in Example 10 of the patents.

In making these allegations, Defendants have ignored the clear evidence of a full disclosure by Amgen. For example, Amgen submitted Dr. Goldwasser's testimony concerning his "abortive trial" to the PTO. Also, Amgen submitted the decision of Judge Harris of the International Trade Commission ("ITC") and discussed his findings with the Examiners. Judge Harris found, based upon the testimony of Dr. Goldwasser and other experts, that the efforts of Goldwasser and others to purify EPO from natural sources such as the urine of patients with

aplastic anemia "yielded only a small amount, barely enough for investigative research and far too little for clinical research into its effectiveness as a treatment for anemia."[1]

Concerning the molecular weight data in Example 10 of the patents, Amgen disclosed to the PTO the data in its possession, including the relevant notebooks of Dr. Egrie. The PTO also had the "Egrie Input" document in its entirety. Concerning the monosaccharide composition data in Example 10, Amgen told the PTO that the data was incorrect and submitted the correct data. The Board of Appeals in the PTO discussed these issues in its decision and, in full view of the allegedly withheld information, held that Amgen had shown sufficient differences in the carbohydrate to support a claim to an EPO glycoprotein product having a different carbohydrate than urinary EPO. Amgen's disclosure and the due consideration given to it by the PTO could not be more plain.

Given the full disclosure by Amgen, Defendants' allegations fail on their face. Suffice it to say, since Amgen disclosed the information, there can be no finding of a withholding of material information with an intent to deceive. Additionally, Defendants have no evidence of either materiality or intent, and certainly not sufficient evidence to carry their heavy burden of clear and convincing evidence. Both the ITC Decision and the PTO decisions in the interferences show the lack of materiality for the allegedly withheld information. In these circumstances, Defendants have advanced a completely baseless defense of inequitable conduct, and summary judgment in favor of Amgen should be granted.

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[1] Initial Determination, *In re Recombinant Erythropoietin*, Investigation No. 337-TA-281 ("ITC Decision"), pp. 51-52, citing to Goldwasser's trial testimony. *See* Exhibit 1 to the Declaration of Richard M. Wong in Support of Amgen's Motion of Summary Judgment ("Decl. of R.Wong") filed herewith. The ITC decision describes the long-felt need for an EPO product to treat anemia – – a need that was resolved only by Dr. Lin's invention and not by the prior efforts of others to purify EPO from urine or blood. This section of the ITC decision, pp. 50-52, was cited to the PTO by Amgen in an amendment

II. Defendants' Amended Answer and Their Inequitable Conduct Allegations

In their Amended Answer,[2] Defendants assert that all five of the patents-in-suit are unenforceable due to acts or omissions which in Defendants' view constitute inequitable conduct. (*See* ¶ 12) However, Defendants fail to identify any particular patent claims that are related to the alleged wrongful acts. In fact, for most of the asserted claims of the patents-in-suit the materiality of the allegedly withheld information is difficult to comprehend. Having had the benefit of full discovery prior to the filing of their Amended Answer, Defendants have no basis for arguing now any additional grounds for materiality.

In paragraph 12(a) of their defenses, Defendants assert that:

- the data from a 1978 Goldwasser study administering urinary-derived EPO ("uEPO") "show[s] that human urinary EPO was effective in stimulating the production of red blood cells;"
- this information is "material to the validity of the patents-in-suit because it is evidence that before the earliest date to which Amgen is entitled, someone else had used biologically active purified human EPO to treat patients;" and
- the Goldwasser Study was material "because during prosecution of Amgen's U.S. Application Serial No. 113,178, the Examiner withdrew claim rejections because '[a]s shown by applicant, urinary EPO lacks in vivo biological activity.'"[3]

Defendants ignore the fact that Amgen did disclose Goldwasser's testimony concerning his failed attempts to treat three patients with uEPO to the PTO. Defendants also ignore that Amgen corrected the Examiner as to the in vivo activity of uEPO at an interview two days later

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dated June 2, 1989 in the prosecution of U.S. Patent Application Serial No. 113,178. *See* Exhibit 2 to Decl. of R. Wong.

[2] Defendants' original Answer to Amgen's Amended Complaint contained only a general pleading of inequitable conduct. Amgen filed a Motion To Strike the defense for failure to comply with the specificity requirement of Rule 9(b) of the Federal Rules of Civil Procedure. In response, Defendants sought leave to file an Amended Answer for the sole purpose of stating with particularity their inequitable conduct allegations. After this Court granted Defendants' motion for leave to amend, TKT/HMR filed their Amended Answer on January 10, 2000. Fact discovery closed on December 1, 1999.

and in its following written submission.[4] In addition, the record of prosecution of the patents is replete with references to the prior art uEPO and the fact that it had biological activity. Equally clear is the fact that uEPO was never available in sufficient quantity or quality to conduct human clinical trials to demonstrate the therapeutic efficacy of EPO to alleviate anemia.

In paragraph 12(b), Defendants allege that:

- Amgen provided the PTO "misleading and incorrect information relating to the comparisons of the molecular weight of CHO-produced recombinant EPO, COS-produced recombinant EPO and urinary EPO that are set out in Example 10 of the patents in suit;" and

- the information in a document entitled "Egrie Input" was withheld. Defendants allege that the "Egrie Input contains data and conclusions inconsistent with the molecular weight comparisons described in Example 10 of the patents in suit."

Defendants ignore the fact that the Egrie Input document was submitted to the PTO and considered in the context of the very same arguments that Defendants raise here. The PTO reviewed the data of Dr. Egrie and concluded that it did not contradict the patent disclosure and that Amgen had made a sufficient showing that recombinant EPO has a different glycosylation from uEPO to provide support for the claimed invention.

Finally, in paragraph 12(c), Defendants assert that:

- Amgen failed to correct "the average carbohydrate composition data in Example 10 of the patents in suit despite learning that the data was incorrect."

In fact, Amgen did tell the PTO that the data was incorrect and did supply the correct data to the PTO. Also, Amgen never attempted to rely upon the incorrect data. While acknowledging the patent data to be erroneous, the PTO still found a difference in the carbohydrate composition

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[3] Amended Answer at p. 14.

[4] "As discussed with the Examiner during the Interview, urinary-derived erythropoietin is active in vivo." Amendment dated 7/12/89, p. 5, Application Serial No. 113,178. Exhibit 3 to Decl. of R.Wong.

between recombinant EPO and uEPO. All of Defendants' allegations are shown to be false by a simple review of the relevant disclosures to the PTO as discussed further in detail below.

III. Statement of Facts Evidencing a Full Disclosure[5]

The following facts are beyond genuine dispute and reveal that Amgen did disclose the allegedly withheld information to the PTO.

Goldwasser Study

In 1988, Dr. Eugene Goldwasser testified in a proceeding before the International Trade Commission involving Amgen's original '008 patent.[6] In that testimony, Dr. Goldwasser described his efforts to obtain EPO from blood and urine and how he was unsuccessful until 1976 when he and his colleague Dr. Miyake purified a small amount of EPO (about 10 milligrams) from over 2500 liters of urine collected from patients with aplastic anemia. Drs. Goldwasser and Miyake published their purification work in 1977.[7] Dr. Goldwasser testified that he used his uEPO to do a study on three patients which showed no therapeutic results:

"Q Well, focusing on this point in time in 1983 or earlier, is it correct that therapeutic amounts of EPO were not available?
A That is absolutely correct.
Q And that is true form any source, whether it is human, or animal, or genetically engineered?
A Very true.
Q Were there adequate amounts of EPO available for investigative or clinical research?

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[5] A separate Statement of Undisputed Facts is filed herewith.

[6] Amgen's first EPO related patent, U.S. 4,703,008 was at issue in the ITC proceeding and in the *Amgen v. Chugai* litigation heard previously in this Court but is not at issue in the present action.

[7] Miyake, et al., *J. Biol. Chem.*, Vol. 252, No. 15 (Aug. 10, 1977) pp. 5558-64 *See* Exhibit 4 to Decl. of R.Wong. This article is discussed in the background section of the patents-in-suit (see '933 patent, Col. 7, lines 10-17). The Court may remember that in the prior litigation with Genetics Institute ("GI") Amgen argued unsuccessfully that the Miyake uEPO anticipated the claims of GI's patent to homogenous EPO. *See* Discussion infra at pp. 15-16.

A Adequate, I would have to say no. **When we finished the purification of the human urinary material, we had enough to do a very limited clinical trial on three patients. But the amount was too small to extend the trial long enough to see any result. So in essence, it was an abortive trial.**
Q Did that limitation of the availability of material have a limiting factor on the research that could progress?
A Yes, it brought our clinical trial to a halt. We just could not do anymore.
Q Was there at that time in your judgment a need for larger amounts erythropoietin?
A Absolutely. **If its potential therapeutic effect were ever to be found out, it needed to have large enough amounts to use relatively large doses in the patient, and to use enough patients to get statistically significant results.**
Q Had that need existed to your knowledge for a long time?
A Ever since the early work on erythropoietin, yes."[8]

In this case, Dr. Goldwasser reaffirmed his prior testimony.[9] Amgen submitted the ITC testimony of Dr. Goldwasser to the PTO pursuant to a Notice under 37 CFR 1.682(a) and characterized it as "relevant as background information and with respect to patentability and Lin's priority case."[10] In so doing, Amgen disclosed the Goldwasser study to the PTO.

The Initial Determination of Judge Harris in the ITC Investigation (the "ITC Decision") discussed the uEPO prior art and the lack of a therapeutically effective product before Dr. Lin's invention. On at least three occasions in the prosecution of the applications resulting in the patents-in-suit, Amgen submitted the ITC Decision to the PTO.[11] The ITC Decision, at pp. 50-52, contained the following analysis of the long felt need for an erythropoietin product to treat anemia:

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[8] Testimony of Dr. E. Goldwasser before ITC in Investigation No. 337-TA-281, pp. 22-23. (Emphasis added). Exhibit 5 to Decl. of R. Wong.

[9] Goldwasser Deposition, Vol. III pp. 317-21., October 14, 1999, *See* Exhibit 6 to Decl. of R. Wong.

[10] Notice (III) By Lin Under 37 CFR 1.682(a) at p. 3, *See* Exhibit 7 to Decl. of R. Wong.

[11] *See* Statement of Undisputed Facts, ¶1.

"The existence of erythropoietin was first postulated in 1906 and evidence proving its existence was published in 1943. Goldwasser, Tr. 8; FF 75. However, the hormone was not purified in an amount sufficient to ascertain some of its chemical and biological properties until Dr. Eugene Goldwasser did so in 1970 after working on the problem for 16 years. Goldwasser, Tr. 11; FF 85.

It has been known since 1957 that EPO is produced in a mammal's kidneys. Eschbach, Tr. 544. Any person that develops advanced renal disease or renal failure will become anemic. Eschbach, Tr. 541.

However, during the 1950's and until the 1980's many researchers believed that there were chemicals present in the blood that acted to inhibit erythropoiesis and cause anemia. Eschbach, Tr. 577; FF 91. Were this so, their presence would blunt the effect of EPO therapy. Id. ***As already noted, prior to the invention of recombinant EPO there was simply not enough EPO available to perform any sort of clinical study into this question. Goldwasser, Tr. 22; FF 97, 98.***

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". . . Early on" in his work, Dr. Goldwasser's clinical colleagues impressed upon him the need for large amounts of exogenous erythropoietin for treatment of the severe anemia suffered by patients with renal disease. Goldwasser, Tr. 12. Efforts were made to obtain purified EPO from natural sources such as the urine of patients with aplastic anemia. FF 87-89. ***However, the result of these efforts yielded a small amount, barely enough for investigative research and far too little for clinical research into its effectiveness as a treatment for anemia. Goldwasser, Tr. 22.*** A program to purify natural EPO from urine of non-anemic persons was a failure because impurities in the urine and in the resulting product made patients sick. Eschbach Tr. 543; CX4-C at 3: FF 84.

Thus, it is evident that since at least the early 1960's the medical community felt a need for a supply of exogenous EPO as an alternative treatment of the anemia suffered by patients with advanced renal disease. In 1983, it had not been possible to meet this need either by isolating natural EPO or by recombinant methods (see discussion on failure of others, infra)."[12]

The ITC Decision, at pp. 89-92, also included the following findings of fact concerning the unsuccessful attempts to isolate and collect therapeutic amounts of natural EPO:

"83. Naturally occurring EPO as produced in the kidneys is present in both the plasma of blood and in urine, but in very low concentrations. Attempts to obtain natural EPO in good yield from these sources proved unsuccessful. (CX-4C at 3)

84. For example, in 1972, the United States government established a program to attempt to purify natural EPO from urine in order to test the therapeutic value of

[12] *See* Exhibit 1 to Decl. of R. Wong, pp. 50-52. (Emphasis added).

EPO in correcting anemia. The experiment was a failure. Impurities in the urine, and corresponding impurities in the purified product, made the patients sick. (Eschbach, Tr. 543)

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88. Dr. Goldwasser, Dr. Miyake and Mr. Kung were unable to produce therapeutically useful amounts of EPO from natural sources. (CX-4C at 6)

89. EPO isolated from patients suffering from aplastic anemia is also not a viable source of EPO for the treatment of patients with anemia. (Shoemaker, Tr. 1003)

90. To conduct large clinical studies to determine the potential therapeutic effect of EPO, large amounts of erythropoietin were required. (Goldwasser, Tr. 23)

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98. ***In sum, prior to 1983, therapeutic amounts of human EPO were not available to conduct clinical trials. (Goldwasser, Tr. 23)***[13]

These findings were based directly on Goldwasser's testimony relating to his failed clinical attempt. Amgen cited to pages 50-52 of the ITC Decision as support for the long felt need for an EPO product that could be used to treat patients with anemia in an amendment dated June 2, 1989 in the prosecution of Application Serial No. 113,178.[14]

Molecular Weight Comparisons

Dr. Joan Egrie, a scientist at Amgen who worked on the EPO project, submitted a declaration to the PTO describing the results of various experiments conducted in 1984 in characterizing the EPO produced as a result of Dr. Lin's inventions.[15] At paragraphs 36-37 of that declaration, Dr. Egrie describes SDS-PAGE experiments conducted by herself and her associates to "determine the size of the recombinant EPO in relation to the EPO in a partially

[13] *See* Exhibit 1 to Decl. of R. Wong, pp. 89-92. (Emphasis added).

[14] *See* Exhibit 2 to Decl. of R. Wong, pp. 5-7.

[15] Declaration of Joan C. Egrie, March 18, 1991. *See* Exhibit 8 to Decl. of R. Wong.

purified pooled source human urinary EPO preparation provided by Dr. Eugene Goldwasser."[16] Dr. Egrie tested EPO produced in both COS cells and CHO cells. Regarding the COS cell produced EPO, Dr. Egrie stated that her results "suggested that the carbohydrate portion of the COS 1 cell-expressed recombinant human EPO and the pooled source human urinary EPO were of approximately the same size."[17]

With respect to CHO cell produced EPO, Dr. Egrie stated at paragraph 36 in her declaration that the results "indicate that the difference in apparent molecular weight observed for the CHO-derived recombinant human EPO and Dr. Goldwasser's partially purified pooled source human urinary EPO is a result of differences in the carbohydrate portion of the molecules."[18]

Amgen submitted copies of Dr. Egrie's Laboratory Notebooks to the PTO. Included in these notebook submissions were SDS-PAGE gels showing comparisons between COS or CHO produced EPO and urinary EPO. For example, Lin Exhibit 115 included pages 65-71 of Egrie Laboratory Notebook 633.[19] Page 69 of this Notebook shows a gel comparing CHO produced EPO with uEPO from Goldwasser and two additional uEPO products labeled "Lot 82" and "Alpha Therapeutics." This same page 69 was included in the document labeled "Egrie Input." Additionally, the Egrie Input document was submitted in its entirety to the PTO,[20] and the PTO

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[16] Id. at p.28

[17] Id. at p.29

[18] Id. at p.30

[19] *See* Exhibit 9 to Decl. of R. Wong.

[20] *See* Exhibit 10 to Decl. of R. Wong, pp. 3 and DX316. The "Egrie Input" document was an exhibit (DX 316) in the prior Boston litigation *Amgen v. Chugai,* and was submitted to the PTO with testimony from Dr. Egrie by the party Fritsch (Genetics Institute).

expressly considered Dr. Egrie's allegedly contradicting gels as stated in the Board's decision in the '334 Interference.[21]

The Monosaccharide Composition Data

In 1991, Amgen told the PTO that: "the hexose values in Example 10 are now seen as probably erroneous. They were believed to be correct by Dr. Lin when Dr. Yu reported them to him (LR 94) and have never been relied on during prosecution to support the assertion of differences in carbohydrate composition."[22] The PTO acknowledged this admission in the Board of Appeal's decision:

> "While Lin concedes that the hexose value reported in his involved applications (Example 10) is probably incorrect, (LB-45). . ."[23]

The correct monosaccharide composition data for CHO-produced EPO and uEPO was submitted to the PTO in at least the following submissions:

- Declaration of Dr. Thomas Strickland dated 4/5/90 which reported the average hexose ratio of six Lots of Amgen's EPO as reported in Amgen's Product License Application. ("PLA")[24]
- Amgen's PLA, pp. 792 and 889-90 provides the complete monosaccharide composition analysis for six lots of Amgen's EPO.[25]
- Sasaki et al., provides a monosaccharide comparison of CHO-produced EPO with uEPO.[26]

[21] *Lin v. Fritsch*, 21 U.S.P.Q.2d 1739, 1741-1742 (Bd. App. 1991). Exhibit 11 to Decl. of R. Wong.

[22] Brief for Senior Party Lin, Exhibit 13 to Dec. of R. Wong p.45. Additionally, Mr. Steven Odre, Amgen's patent counsel, testified upon deposition that he told the Examiner in 1988 at an interview that the monosaccharide composition data reported in Example 10 were not to be relied upon in showing glycosylation differences. See Odre Deposition, February 14, 2000, pp. 82-83, Exhibit 12 to Decl. of R. Wong.

[23] *Fritsch v. Lin*, 21 U.S.P.Q.2d at 1741, Exhibit 11 to Decl. of R. Wong.

[24] *See* Exhibit 14 to Decl. of R. Wong, pp. 7-8.

[25] *See* Exhibit 15 to Decl. of R. Wong submitted by both Lin and Fritsch.

[26] *See* Exhibit 16 to Decl. of R. Wong, submitted as Lin Exhibit 214 in the Interferences.

Thus, the PTO knew about the erroneous data in the patent and Amgen submitted the correct monosaccharide composition data. As shown below, the PTO found sufficient evidence of differences in glycosylation despite the erroneous monosaccharride data.

IV. Legal Standards

A. Summary Judgment

Summary judgment is appropriate if "there is no genuine issue as to any material fact and . . . the moving party is entitled to a judgment as a matter of law."[27] "A 'genuine' issue of fact is one that a reasonable jury, on the record before the court, could resolve in favor of the non-moving party."[28] As this Court has previously recognized, "If there are no genuine issues of material fact, summary judgment is appropriate in a patent infringement case as in any other."[29]

B. Inequitable Conduct

Inequitable conduct can be based upon the failure to disclose material information or the submission of material false information to the PTO with the intent to deceive or mislead.[30] "Both materiality and intent must be proven by clear and convincing evidence."[31] That is, Defendants must prove by clear and convincing evidence that Amgen failed to disclose material

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[27] Fed. R. Civ. P. 56(c). *See London v. Carson Pirie Scott & Co.*, 946 F.2d 1534, 1537-38 (Fed. Cir. 1991).

[28] *Giese v. Pierce Chemical Co. et al.*, 43 F.Supp.2d 98, 101-02 (D.Mass. 1999) citing *Anderson v. Liberty Lobby, Inc.* 477 US; 242, 248-49, 91 L.Ed.2d 202, 106 S.Ct. 2505 (1986).

[29] *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104, 106-7, (D. Mass. 1998) (citing *Moeller v. Ionetics, Inc.*, 794 F.2d 653, 656 (Fed. Cir. 1986)).

[30] *Litton Systems, Inc. v. Honeywell, Inc.*, 87 F.3d 1559, 1570 (Fed. Cir. 1996), vacated on other grounds, 520 U.S. 1111 (1997).

[31] Id. at 1570.

information to the Patent Office and that Amgen did so with the specific intent of deceiving the Patent Office. Defendants can prove none of these facts.

While most reported decisions involving the issue of inequitable conduct focus on the materiality requirement and/or the intent requirement, the present case presents a much simpler issue: there can be no inequitable conduct for failing to disclose material information when the evidence plainly demonstrates that the information alleged to be withheld **was, in fact, disclosed** to the Patent Office.[32]

V. The Court Should Enter Summary Judgment of No Inequitable Conduct

A. The Goldwasser Study and its results were disclosed to the PTO and only confirm the validity of the Amgen Patents.

Defendants' assertions that Amgen withheld information about the Goldwasser study from the PTO are plainly incorrect. First, Amgen disclosed the prior art uEPO publications, including the Miyake publication, and discussed them with the Examiners. Second, Amgen submitted Dr. Goldwasser's testimony concerning his failed clinical attempt using his uEPO as evidence during the Interferences with GI. Third, Amgen submitted the ITC Decision, which summarized Dr. Goldwasser's testimony, during the prosecution of the applications leading to the patents-in-suit. Thus, contrary to Defendants' assertions, the Goldwasser study was disclosed to and known by the PTO, as were the results.

[32] *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1582, (Fed. Cir. 1991) ("When a reference was before the examiner, whether through the examiner's search or the applicant's disclosure, it can not be deemed to have been withheld from the examiner.")

As stated in the ITC Decision, as of 1983 there existed a long felt need for a therapeutically useful EPO product available in sufficient quantity and quality to treat anemic patients. The prior attempts to isolate EPO from blood or urine did not meet this need:

> "Efforts were made to obtain purified EPO from natural sources such as the urine of patients with aplastic anemia. However, the result of these efforts yielded a small amount, barely enough for investigative research and far too little for clinical research into its effectiveness as a treatment for anemia."[33]

Thus, the ITC Decision concluded that "Dr. Goldwasser, Dr. Miyake and Mr. Kung were unable to produce therapeutically useful amounts of EPO from natural sources."[34]

Defendants assert that the Goldwasser study is material to the patents-in-suit because the data showed that "human urinary EPO was effective in stimulating the production of red blood cells." This statement simply repeats the known biological activity of EPO as set forth in the background section of the patent and does not show any materiality for the Goldwasser study.[35] The patents-in-suit do not claim uEPO; rather, Dr. Lin's invention was a pharmaceutical composition comprising a therapeutically effective amount of human EPO.[36] The issue, then is not whether uEPO has the biological activity of stimulating the production of red blood cells, but whether Goldwasser's uEPO could be used therapeutically and whether there were sufficient amounts available to treat patients long enough to achieve a therapeutic effect. Clearly, uEPO

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[33] *Id.* at 51-52; also, Findings of Fact, ¶¶ 86-88 (discussing Goldwasser testimony); Findings of Fact, ¶ 88 (discussing Goldwasser testimony and related documents).

[34] Id., Findings of Fact ¶ 88-90.

[35] '933 Patent, Col. 5, line 39-Col. 6, line 59.

[36] *See* the '422 patent claims 1 and 2. Claim 2 is not at issue in this litigation and Claim 1 is directed to human EPO purified from mammalian cells grown in culture.

was not available in such amounts nor was it shown in the Goldwasser study to have the therapeutic effect of alleviating anemia.[37]

Further, Defendants incorrectly argue that the Examiner withdrew claim rejections based upon his misunderstanding of this issue: "[a]s shown by applicant, urinary EPO lacks in vivo biological activity"[38] However, Amgen corrected the Examiner's misstatement, in an interview two days later and in its next written response: "As discussed with the Examiner during the interview, urinary-derived erythropoietin is active in vivo."[39]

Defendants' allegation that the Goldwasser study is material because it "evidenced" that prior to Dr. Lin's inventions "someone else had used biologically active purified human EPO to treat patients" is similarly misplaced. Dr. Goldwasser's testimony contradicts this position:

> **"When we finished the purification of the human urinary material, we had enough to do a very limited clinical trial on three patients. But the amount was too small to extend the trial long enough to see any results. So in essence, it was an abortive trial."**[40]

Amgen certainly had no information to disagree with Dr. Goldwasser's conclusions. The October 31, 1990 Egrie memorandum referenced in the Amended Answer (at ¶12(a)) contained hand-written (and nearly illegible) raw patient data which showed no increase in hematocrit over the course of treatment. As Defendants' witnesses Drs. Hahner and Means agree, the clinical measure of therapeutic efficacy in the treatment of anemia is an increase in hematocrit.[41,42]

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[37] The Goldwasser study showed no significant increase in the hematocrit of the three patients. *See* Statement of Undisputed Facts, ¶8. Hematocrit (like the corresponding measure of hemoglobin) is a measure of the amount of red blood cells in the blood.

[38] Amended Answer at p.14.

[39] USSN 113,178, Amendment 7/11/89, p.5, Exhibit 3 to Decl. of R. Wong. (Emphasis in original).

[40] *See* Exhibit 5 to Decl. of R. Wong, p.23. (Emphasis added).

[41] Dr. Hahner depo., pp. 247, 419-423, 466-467, Exhibit 23 to Decl. of R. Wong; Means depo., pp. 13, 115-116. Exhibit 24 to Decl. of R. Wong.

The issue whether the uEPO purified by Drs. Goldwasser and Miyake was useful as a therapeutic product was also previously addressed by this Court in the *Amgen v. Chugai* litigation. Although the Goldwasser/Miyake uEPO was the most purified and exhibited the highest specific activity of any uEPO preparation known in 1983, it was not as active as recombinant EPO. Even though Amgen consistently argued that it was purified to homogeneity, this Court in 1989 found that the Goldwasser/Miyake uEPO was not "homogeneous" and thus not useful therapeutically:

> "Regardless of the source, however, the erythropoietin protein must be purified to homogeneity in order to use it therapeutically.
>
> It had been thought in the scientific community that erythropoietin purified by methods described by Miyake was homogeneous as measured by a specific activity on the order of 80,000 International Units (IU) per absorbance unit (AU) at 280 nanometers (A280) (hereinafter, "IU/AU"). Dr. Rodney Hewick ("Dr. Hewick"), however, discovered that truly homogeneous erythropoietin has a specific activity of at least about 160,000 IU/AU and, further, that Miyake's erythropoietin composition is not in fact homogeneous, but contains large amounts of several non-erythropoietin protein contaminants."[43]

Similarly, after trial, Judge Saris held:

> "Amgen argues that 'homogenous' EPO was made in Dr. Goldwasser's laboratory in 1976, and that this was a prior invention of the subject matter in the '195 patent product claims. However, Amgen has not shown by clear and

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[42] Defendants argue that the patent provides a different test for therapeutic effect in treating anemic patients than is accepted in the medical profession. Defendants construe the patent as defining "therapeutic effect" as including any biological response to the EPO, e.g., an increase in reticulocytes (or immature red blood cells) and assert that the Goldwasser Study showed such a response. This position, however, is based upon a misreading of the patent. At Col. 12, lines 1-7, the patent clearly describes pharmaceutical compositions "which allow for provision of erythropoietin therapy, especially in the treatment of anemic disease states and most especially such anemic states as attend chronic renal failure." At Col. 33, lines 14-48, the portion cited by Defendants, the patent broadly describes the different disease states that are treatable using EPO of the invention, and that such EPO products "are conspicuously suitable for use in erythropoietin therapy procedures" by drawing upon the known biological activity of EPO. Contrary to Defendants' view, this description does not alter the normally held view of what constitutes a "therapeutic effect." For anemic patients, it means that you treat their anemia by achieving an increase in hematocrit.

[43] Mem. and Order 1/31/89, *Amgen v. Chugai*, Civil Action No. 87-2617-Y, (footnotes omitted). Exhibit 17 to Decl. of R. Wong.

convincing evidence that Fraction II or III of the Miyake Sample of June 30, 1976 was homogeneous."[44]

On appeal, the Federal Circuit did not address this anticipation issue but held the GI '195 patent invalid for lack of enablement because the '195 patent did not provide a way to achieve the claimed invention.[45]

Thus, the ITC Decision and the prior decisions of this Court established that the Goldwasser uEPO was not useful as a therapeutic product. Given the conclusions of the Courts, it would have been misleading for Amgen to submit information to the PTO that uEPO was a therapeutic product. The disclosures made by Amgen to the PTO, the ITC Decision, and this Court's prior decisions preclude a finding of materiality or intent to deceive the PTO by any alleged withholding of any information regarding the Goldwasser Study.

B. The Patent Office had full knowledge of the Egrie molecular weight comparison data during the prosecution of the patents.

As a second basis for inequitable conduct, Defendants allege that the Egrie input document was withheld from the PTO and that it "contains data and conclusions inconsistent with the molecular weight comparisons described in Example 10 of the patents in suit."[46] Contrary to Defendants' allegations, the work of Dr. Egrie was submitted to the PTO in the Interferences by way of: (1) her declaration and attached exhibits; (2) her laboratory notebooks; and (3) her deposition testimony and referenced exhibits from the Boston litigation. The Egrie Input document was submitted both in its entirety and as pages from Dr. Egrie's laboratory

[44] *Amgen v. Chugai*, 13 U.S.P.Q.2d 1737, 1783 (D.Mass. 1989), Exhibit 18 to Decl. of R. Wong. The District Court decision was submitted to the PTO. *See* Exhibit 26 to Decl. of R. Wong.

[45] *Amgen v. Chugai*, 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991), Exhibit 19 to Decl. of R. Wong.

[46] Amended Answer at pp. 14-15.

notebooks.[47] Consequently, the Egrie Input was not withheld from the PTO and certainly was not "willfully withheld" as asserted by Defendants.

Also contrary to Defendants' assertions, the PTO has already considered the Egrie Input and found that it does not contradict the molecular weight comparison reported in the patents. The Board of Appeals decision in the '334 Interference makes clear that this information was disclosed and its significance considered during the interference. In the '344 Interference, Genetics Institute, through its inventor Dr. Fritsch, raised the same arguments now raised by Defendants — that the Egrie work showed that rEPO migrated identically with uEPO samples on SDS-PAGE thereby contradicting the disclosure in the patent:

> "Third, the primary examiner was not informed of an SDS PAGE gel prepared by Amgen's Dr. Egrie in September 1984, two months before Lin's involved application was filed, in which two different uEPO samples were compared with Lin's rEPO. The rEPO sample migrated identically with the uEPO samples on the gel, clearly contradicting the import of the disclosure at p. 64, line 20 to p. 65, line 3 of the Lin application of an apparent difference in molecular weight between rEPO and uEPO. *See* Finding VI-17."[48]

In the Proposed Findings VI-17, Fritsch specifically pointed to the gel comparing CHO rEPO with Alpha Therapeutics and Lot 82 EPO contained in the Egrie Input (LNB 633, p. 69):

> "Moreover, an entry in Dr. Egrie's own notebook No. 633 dated 9 /19-9/21/84 states that Amgen's rEPO appeared to be the same size as uEPO sample obtained from Alpha Therapeutics and a uEPO sample designated as "Lot 82." LX 115, (doc. no. L01074). Dr. Egrie has acknowledged that the uEPO and rEPO samples migrated identically on the SDS-polyacrylamide gel. LR 577-579 (Egrie). Because all known uEPO samples are prepared from pooled sources, as was the uEPO referenced in Example 10, the unequal-weight observations described in Example 10 of the Lin application are clearly contradicted by the Egrie notebook data."[49]

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[47] Statement of Undisputed Facts, ¶¶ 11-12.

[48] Reply Brief of the Party Fritsch p. 36, citing to Finding VI-17, *See* Exhibit 20 to Decl. of R. Wong.

[49] Excerpts of the Proposed Findings of Fact and Conclusions of Law for Party Fritsch, *See* Exhibit 21 to Decl. of R. Wong.

In its decision, the Board cited to the results reported in the patent of differences on SDS-PAGE and found that these results supported a claim to differences in carbohydrate composition:

> "Specifically, we note that Lin's involved application, in addition to including the disputed hexose molar ratio data, also reports results of Western blot and SDS-PAGE analyses said to indicate that r-EPO had a somewhat higher molecular weight than u-EPO. These, coupled with the additionally disclosed results of endoglycosidase F enzyme treatment which indicate that the non-carbohydrate component of r-EPO and u-EPO have 'essentially identical molecular weight characteristics,' support the conclusion that there is indeed a difference in carbohydrate composition (see the paragraph bridging pages 64-65 in Lin's involved application)."[50]

The Board then reviewed Egrie's SDS-PAGE results as argued by Fritsch and held:

> In our view, the Egrie testimony, which is cited in Fritsch's Reply Brief (FRB-36) is at best ambiguous and, thus, is not sufficient to contradict the information disclosed on page 64 of the Lin application. In this regard, Dr. Egrie of Amgen admits only that certain u-EPO and r-EPO examples which she studied by Western blot had "approximately the same size". When asked whether this comparative "size" data are indicative of the same carbohydrate composition, she responded: "No. Not necessarily at all."[51]

Again, there is no question that the Patent Office had before it the information contained in the Egrie Input document and that the PTO found it not to contradict the disclosure of the patent. Subsequent Examiners in the continued prosecution of the Lin patent applications after the termination of the three interferences would have known of the Board's decision and were bound by it.[52] Defendants' allegations that material information was withheld with an intent to deceive the PTO are completely unfounded.

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[50] *Fritsch v. Lin*, 21 U.S.P.Q.2d 1739, 1741-42, (Bd. App. 1991) citing to Col. 28, lines 33-50 of the '933 patent. Exhibit 11 to Decl. of R. Wong.

[51] *Fritsch v. Lin*, 21 U.S.P.Q.2d at 1742. Exhibit 11 to Decl. of R. Wong.

[52] *See* Expert Declaration and Report of John T. Goolkasian Regarding Inequitable Conduct, ¶¶ 5-10, attached as Exhibit 22 to Decl. of R. Wong.

C. The Patent Office had full knowledge of the error in the monosaccharide composition data during the prosecution of the patents.

Defendants allege that Amgen failed to inform the Examiner that the monosaccharide composition data reported in Example 10 (at Col. 28, lines 51-67) is incorrect and that Amgen should have corrected the data.[53] Again, Defendants' allegations are completely at odds with the record of prosecution of the patents. In fact, Amgen told the PTO that the data was wrong and submitted correct data for the PTO's consideration.[54]

On the face of its decision in the '334 Interference, the Board noted Lin's concession that the data was erroneous.[55] The Board then noted that the SDS-PAGE data reported in the patent supported a finding of differences in the carbohydrate between r-EPO and u-EPO. In addition, the Board considered further evidence submitted in the record that showed differences. Particularly, the Board cited to Amgen's PLA pages 791-800. On page 792 of the PLA, the results of compositional analyses of several different lots of Amgen's r-EPO are discussed and reference is made to Figure 9.C-1 which records the data.[56] Consequently, the PTO was told of the error, given the correct data and the Board clearly considered it in rendering its decision.

The "fundamental question" addressed in the '334 Interference was "whether the average carbohydrate composition of the r-EPO enabled by the Lin disclosure in fact differs from that of naturally occurring human urinary EPO (u-EPO)."[57] Again, Fritsch presented the same

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[53] Amended Answer at pp. 15-16.

[54] *See* Statement of Undisputed Facts, at ¶¶ 15-18.

[55] "Lin concedes that the hexose value reported in his involved application (Example 10) is probably incorrect...." *Fritsch v. Lin*, 21 U.S.P.Q.2d 1739 at 1741. Exhibit 11 to Decl. of R. Wong.

[56] *See* Exhibit 15 to Decl. of R. Wong. Figure 9.C-1 is shown on pp. 889-90 of the PLA.

[57] *Lin*, 21 U.S.P.Q.2d at 1741. Exhibit 11 to Decl. of R. Wong.

arguments Defendants raise here concerning the erroneous hexose data.[58] In the face of these arguments, the Board held that Amgen was entitled to patent claims to a "a non-naturally occurring" EPO product having a difference in carbohydrate composition from uEPO.

VI. Conclusion

Since Defendants' allegations of inequitable conduct are unfounded, and Amgen is entitled to judgment as a matter of law, summary judgment should be granted in favor of Amgen on the defense of unenforceability due to inequitable conduct.

Dated: February 23, 2000

For the Plaintiff AMGEN INC.

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CERTIFICATE OF SERVICE
I hereby certify that a true copy of the above document was served upon the attorney of record for each other party by mail-hand on Feb 23, 2000

[58] *See* Fritsch Reply Brief ¶¶ 35-36, Exhibit 20 to Decl. of R. Wong.