In the Matter of

CERTAIN RECOMBINANT ERYTHROPOIETIN

Investigation No. 337-TA-281
(Decision of April 10, 1989)

USITC PUBLICATION 2186

MAY 1989

United States International Trade Commission
Washington, DC 20436

UNITED STATES INTERNATIONAL TRADE COMMISSION

COMMISSIONERS

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Washington, DC 20436

APR 10 1989
OFFICE OF THE SECRETARY
U.S. INTL. TRADE COMMISSION

UNITED STATES INTERNATIONAL TRADE COMMISSION
Washington, DC 20436

In the Matter of CERTAIN RECOMBINANT ERYTHROPOIETIN	) Investigation No. 337-TA-281

NOTICE OF COMMISSION DECISION TO DISMISS COMPLAINT FOR LACK OF SUBJECT MATTER JURISDICTION AND TO TERMINATE THE INVESTIGATION

AGENCY: U.S. International Trade Commission

ACTION: Notice

SUMMARY: Notice is hereby given that the U.S. International Trade Commission has determined to dismiss the complaint for lack of subject matter jurisdiction and to terminate the investigation.

ADDRESS: Copies of the Commission's Order, the Commission's opinions, the presiding ALJ's final initial determination (ID), and all other non-confidential documents filed in connection with this investigation are available for inspection during official business hours (8:45 a.m. to 5:15 p.m.) in the Office of the Secretary, U.S. International Trade Commission, 500 E Street SW., Washington, DC 20436, telephone 202-252-1000.

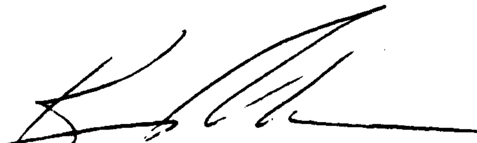
FOR FURTHER INFORMATION CONTACT: Jean Jackson, Esq., Office of the General Counsel, U.S. International Trade Commission, telephone 202-252-1104. Hearing-impaired individuals are advised that information on this matter can be obtained by contacting the Commission's TDD terminal on 202-252-1810.

SUPPLEMENTARY INFORMATION: On February 10, 1988, the Commission instituted an investigation to determine whether there is a violation of section 337 of the Tariff Act of 1930 in the importation or sale of certain recombinant erythropoietin by reason of alleged unfair acts in the importation into and sale in the United States of recombinant erythropoietin manufactured abroad by a process which, if practiced in the United States, would infringe claims 2, 4-7, 23-25, and 27-29 of U.S. Letters Patent 4,703,008. The Commission named Chugai Pharmaceutical Co., Ltd. of Japan and Chugai, USA, Inc. of New York City as respondents. During the investigation, the Commission granted a motion filed by The UpJohn Company of Kalamazoo, Michigan, to intervene as a respondent.

On January 10, 1989, the presiding administrative law judge issued his final ID finding no violation of section 337. On February 27, 1989, the Commission determined to review the ID in its entirety.

This action is taken under authority of section 337 of the Tariff Act of 1930 (19 U.S.C. 1337) and section 210.56 of the Comission's interim rules (53 Fed. Reg. 33071 (Aug. 29, 1988)).

By order of the Commission.



Kenneth R. Mason
Secretary

Issued: April 10, 1989

UNITED STATES INTERNATINAL TRADE COMMISSION
Washington, DC 20436

In the Matter of CERTAIN RECOMBINANT ERYTHROPOIETIN	)	Investigation No. 337-TA-281

ORDER TERMINATING INVESTIGATION

Having examined the record in this investigation, and determining that the Commission does not have subject matter jurisdiction over the complaint filed in the above-captioned investigation under section 337 of the Tariff Act of 1930 (19 U.S.C. 1337), it is hereby ORDERED:

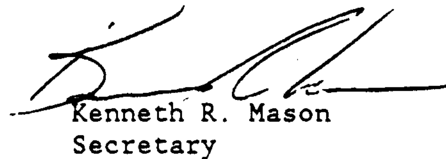
1. The complaint is dismissed for lack of subject matter jurisdiction;

2. The investigation is terminated;

3. Notice of this Order shall be published in the Federal Register; and

4. The Secretary shall serve copies of this Order and the Commission Opinions issued in this investigation on each party of record to this investigation and on the Department of Health and Human Services, the Department of Justice, the Federal Trade Commission, and the Secretary of the Treasury.

By order of the Commission.



Kenneth R. Mason
Secretary

Issued: April 10, 1989

UNITED STATES INTERNATIONAL TRADE COMMISSION
Washington, D.C. 20436

In the Matter of CERTAIN RECOMBINANT ERYTHROPOIETIN	)))))	Investigation No. 337-TA-281

COMMISSION OPINION 1/

Views of Commissioners Eckes, Lodwick, Rohr, and Newquist 2/

INTRODUCTION

The subject investigation is based on a complaint filed under section 337 of the Tariff Act of 1930 (19 U.S.C. 1337) alleging unfair practices in the importation and sale of recombinant erythropoietin. The unfair practice alleged by complainant Amgen, Inc. (Amgen) was violation of 19 U.S.C. 1337a in the importation of recombinant erythropoietin manufactured by a process which,

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1/ The following abbreviations are used in this opinion: ALJ = Administrative Law Judge; CX = Complainant's Exhibit; FF = Finding of Fact; ID = Initial Determination: Tr. = Transcript of the evidentiary hearing.

2/ See Views of Chairman Brunsdale and Vice Chairman Cass.

if practiced in the United States, would infringe claims 2, 4-7, 23-25, or 27-29 of U.S. Letters Patent 4,703,008 (the '008 patent) owned by Amgen. 3/ 4/

Chugai Pharmaceutical Co., Ltd. and Chugai U.S.A., Inc. (Chugai) were named as respondents in this investigation. The Upjohn Company was permitted to intervene as a respondent in the economic phase of the investigation. On January 10, 1989, the presiding administrative law judge (ALJ) filed his final initial determination (ID) finding no violation of section 337. 5/ On February 27, 1989, the Commission determined to review the ID in its entirety.

SUMMARY OF THE ID

The ID concluded that the Commission has jurisdiction over the investigation under section 337(a)(1)(B)(ii). The ID determined that the Chugai respondents had not overcome the statutory presumption of validity that attaches to the '008 patent as a duly issued U. S. patent, nor had they shown

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3/ The complaint was filed before passage of the Omnibus Trade and Competitiveness Act of 1988 (OTCA), which recodified 19 U.S.C. 1337a as section 337(a)(1)(B)(ii) without substantive change. In the interest of clarity, this opinion will use the new section designation unless the discussion concerns only former 19 U.S.C. 1337a.

4/ Amgen's complaint also alleged that the effect and tendency of this importation was to substantially injure an efficiently and economically operated domestic industry, and/or to prevent the establishment of such an industry in the United States. The amendments to the section 337 effected by the OTCA eliminated the requirements of showing injury and economic and efficient operation in patent-based cases. The OTCA amendments are applicable to investigations, such as Erythropoietin, that were pending at the time the OTCA became law.

5/ The procedural history of this investigation is set forth in the ID at pp. 2-9.

that the '008 patent was unenforceable due to inequitable conduct by the patent applicant before the U.S. Patent and Trademark Office (PTO). The ID determined that Chugai uses host cells that come within the scope of the '008 patent in Japan to produce recombinant erythropoietin. However, because Chugai's activities occur outside the United States, the ID found that Chugai's activities do not constitute patent infringement under Deepsouth Packing v. Laitram Corp., 406 U.S. 518 (1972).

The ID granted complainant Amgen's motion for summary determination of the issue of domestic industry, finding that Amgen had demonstrated beyond reasonable controversy the existence of significant investment in plant and equipment with respect to the articles protected by the asserted patent. 6/

DISCUSSION

I. Product Under Investigation

The product under investigation is a prescription drug called recombinant erythropoietin. The drug is administered to patients suffering from anemia (red blood cell deficiency) associated with chronic kidney disease. Natural erythropoietin is a hormone that controls the synthesis of red blood cells in

6/ The ID also declassified certain documents that the Chugai respondents had designated "confidential." On February 15, 1989, the Commission issued an order staying the release of those documents pending either the completion of an appeal to the Court of Appeals for the Federal Circuit by Chugai or the expiration of time for filing such an appeal. The Commission's stay is in effect pending the Commission's disposition of Amgen's motion for reconsideration of the Commission's order of February 15, 1989.

the bone marrow. Although present in urine and blood, the concentration of natural erythropoietin is extremely low. This low concentration makes purification of the hormone from natural sources impractical. Consequently, naturally-derived erythropoietin is not available for medical treatment of anemia.

Recombinant erythropoietin (hereinafter "EPO") is produced by culturing altered living cells, known as host cells, in the laboratory. "Recombinant" refers to the method by which the cells are altered. DNA, organized in a gene, is taken from another type of cell and recombined with the DNA naturally present in a host cell. The host cell is then endowed with characteristics coded for by the "foreign" gene. In the case of EPO, the human gene containing the information for the production of the hormone EPO is placed into the chromosome of the host cell. The host cell is then capable of producing human EPO. Because the host cells do not have natural feedback mechanisms to control the level of EPO production, they produce EPO at much higher rates than normal human cells. EPO is excreted from the host cells into the growth medium surrounding the cells. Separation techniques are used to purify EPO from the medium.

II. The Patent

The '008 patent issued on October 27, 1987, and will expire on that date in 2004. It claims recombinant DNA sequences, vectors, and host cells that are used to produce the product EPO. The '008 patent does not claim the

product EPO. The following claims are representative:

> Claim 2. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin.
>
> Claim 5. A biologically functional circular plasmid or viral DNA vector including a DNA sequence according to claim 1, 2, or 3.
>
> Claim 23. A procaryotic or eucaryotic cell transformed or transfected with a DNA sequence according to claim 7, 8, or 11 in a manner allowing the host cell to express said polypeptide [i.e., erythropoietin].

III. The Scope of Investigation

The Commission's notice of investigation stated that the scope of the investigation was:

> . . . whether there is a violation of subsection a of section 337 in the unlawful importation into and sale in the United States of certain recombinant erythropoietin manufactured abroad by a process which, if practiced in the United States, would infringe claims 2, 4-7, 23-25, or 27-29 of U.S. Letters Patent 4,370,008 . . . .

53 Fed. Reg. 3948 (Feb. 10, 1988)(emphasis added).

The Commission has traditionally used the underlined language, which is not found in section 337, to define the scope of investigations alleging violations of section 337(a)(1)(B)(ii). 7/ The Commission has used this language in notices of investigation only when the asserted patent claims

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7/ See, e.g. 52 Fed. Reg. 15568 (April 29, 1987)(Certain Reclosable Plastic Bags and Process for the Manufacture Thereof, Inv. No. 337-TA-266); 51 Fed. Reg. 46944 (Dec. 29, 1986)(Feathered Furs Coats and Process for Manufacture Thereof)); 51 Fed. Reg. 22144 (June 18, 1986), Plastic Fasteners and Processes for the Manufacture Thereof, Inv. No. 337-TA-248).

covered a process or processes. 8/ The Commission has never intended to suggest by this language that it considers the use of a process abroad that employs an article protected by a U.S. patent to be a violation of U.S. patent law or section 337(a)(1)(B)(ii).

IV. Jurisdiction Under Section 337(a)(1)(B)(ii)

The only basis for jurisdiction asserted by Amgen during this investigation was subsection 337(a)(1)(B)(ii). 9/ Section 337, as amended, provides in pertinent part:

> (a)(1) Subject to paragraph (2), the following are unlawful, and when found by the Commission to exist shall be dealt with, in addition to any other provision of law, as provided in this section:
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> * * *
>
> (B) The importation into the United States, the sale for importation, or the sale within the United States after importation by the owner, importer, or consignee, of articles that---
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> * * *
>
> (ii) are made, produced, processed, or mined under, or by means of, a process covered by the claims of a valid and enforceable United States patent.

8/ The notice in this investigation is not an exception to this rule because complainant Amgen alleged that the '008 patent claims covered processes.

9/ Early in the investigation the Chugai respondents challenged the subject matter jurisdiction alleged by Amgen by filing a motion for summary determination of no subject matter jurisdiction. The only basis for jurisdiction argued by Amgen in responding to Chugai's motion was subsection 337(a)(1)(B)(ii). The ALJ denied Chugai's motion as well as Chugai's request to file an interlocutory appeal of the ALJ's decision with the Commission.

The ID contains a thorough analysis of the language and legislative history of former 19 U.S.C. 1337a, the predecessor of section 337(a)(1)(B)(ii). 10/ We adopt that portion of the ID. 11/ Based on the analysis of subsection 337(a)(1)(B)(ii) found in the ID, we conclude that the existence of a process patent claim is required for invoking the jurisdiction of subsection 337(a)(1)(B)(ii).

V. Coverage of the '008 claims

All parties to this investigation agreed that the claims of the '008 patent include sequences of DNA that code for human EPO, plasmids or vectors that contain the DNA sequences, and host cells that are "transfected" with DNA sequences "in a manner allowing the host cells to express" EPO. Complainant Amgen conceded that the '008 patent does not contain what Amgen refers to as "traditional process claims," but asserted that because the '008 claims were drawn to "living, dynamic host cells," they were unique "hybrid" claims covering both articles (the cells) and intracellular processes (*i.e.*, the thousands of chemical processes that take place within a living cell). Amgen

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10/ Because the OTCA recodified 19 U.S.C. 1337a as 337(a)(1)(B)(ii) without substantive change or comment, the ID appropriately examined the language and legislative history of 19 U.S.C. 1337a in interpreting section 337(a)(1)(B)(ii).

11/ ID at 17-21 and Appendix A.

did not support this argument with any citation to statutory or case law. 12/

The ID determined that the '008 claims do not cover any processes. The ID's determination is based on: (1) the cancellation of certain process claims during prosecution of the '008 patent at the PTO, (2) the inventor's testimony that he did not invent the intracellular processes, and (3) the inventor's failure to point out where the claims or the specification indicated that the inventor was claiming the intracellular processes. 13/ We adopt the ID's finding that the '008 patent does not claim a process. However, we base our determination on principles of claim interpretation. 14/

As originally filed, the '008 patent application contained claims 69-72. Those claims were drawn to growing transfected cells in an appropriate culture medium and then isolating the EPO from the culture medium. The type of processes recited in claims 69-72 were directed to extracellular processes,

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12/ We note that the PTO does not recognize "hybrid" claims. Rzucidlo Affidavit, par. 7, dated Feb. 11, 1988. Moreover, both the U.S. Court of Customs and Patent Appeals, one of the predecessors of the U.S. Court of Appeals for the Federal Circuit, and the Supreme Court have held that the fact that an invention may be living has no legal significance. In re Bergy, 596 F.2d 952, 975 (CCPA 1979), aff'd sub nom. Diamond v. Chakrabarty, 447 U.S. 303 (1980); in accord Diamond v. Chakrabarty, 447 U.S. 303, 313.

13/ ID at 24-25.

14/ The inventor's testimony is normally not considered a basis for claim interpretation. Claim interpretation is based on the language of the patent claims, the content of the patent specification, and the patent's prosecution history. Autogiro Company v. United States, 384 F.2d. 391, 397-398 (Ct. Cl. 1967); Loctite Corp. v. Ultraseal Ltd., 781 F.2d 861, 867 (Fed. Cir 1985). When the meaning of key terms used in the claims is in dispute, testimony from witnesses may be adduced. Tandon Corp. v. U.S. International Trade Commission, 831 F.2d 1017, 1021 (Fed. Cir. 1987).

i.e., the steps done by man that occur outside the living cell. 15/ The PTO examiner rejected claims 69-72 as obvious under 35 U.S.C. 103 in view of known processes that entailed growing other types of host cells to produce other types of proteins. In response to the rejection, Amgen did not try to overcome the examiner's obviousness rejection, but instead amended its application by rewriting its article claims and cancelling the disputed process claims. 16/ In its amendment, Amgen stated that none of the rewritten claims corresponded to the cancelled process claims and, therefore, the issue of whether the process claims were patentable over the prior art was no longer present. 17/

It is a fundamental principle of patent law that the claims of a patent must be construed in light of the prosecution history. SRI International v. Matsushita Elec. Corp. of America, 775 F.2d 1107, 1118 (Fed. Cir. 1985).

15/ Claim 70 is representative:

> 70. A process for the production of a polypeptide having part or all of the primary structural conformation and one or more of the biological activities of naturally-occurring erythropoietin, said process comprising:
>
> growing, under suitable nutrient conditions, procaryotic or eucaryotic host cells transformed or transfected with a DNA vector according to claim 63, and isolating desired polypeptide products of the expression of DNA sequences in said vector. (CX-2 at 141).

16/ In its response to the PTO action, Amgen stated that it intended to file a continuing application containing the rejected process claims. CX-2 (file wrapper of the '008 patent) at 341-345.

17/ CX-2 at 367, See also FF 324.

Moreover, a patentee is precluded from "obtaining a claim construction that would resurrect subject matter surrendered during prosecution of his patent application." Thomas & Betts Corp. v. Litton Systems, Inc., 720 F.2d 1572, 1579 (Fed. Cir. 1983)(citing Hughes Aircraft Co. v. United States, 717 F.2d 1351, 1362 (Fed. Cir. 1983); Schriber-Schroth Co. v. Cleveland Trust Co., 311 U.S. 211, 218 (1940)(abandoned claims cannot be revived by reading them by construction into issued claims); Arco Indus. v. Chemicast, 633 F.2d 435, 440-41 (6th Cir. 1980)(a claim cannot be construed to revive rejected or abandoned claims).

The ALJ found that the process of growing a transfected host cell and isolating the protein must necessarily include all of the intracellular processes that are involved in producing EPO. 18/ We adopt that finding. Accordingly, when Amgen cancelled its process claims directed to growing the cells and isolating the EPO, it also foreclosed itself from later asserting that claims to the intracellular processes were preserved in the issued claims.

The intracellular processes that Amgen alleges are covered by the '008 patent claims occur naturally once the DNA coding for EPO is placed in the host cell. 19/ The '008 claims cannot, as a matter of law, cover these intracellular processes because under 35 U.S.C. 101 "whoever invents . . . is

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18/ ID at 24.

19/ CX-1 (the '008 patent) at col. 2.; Tr. 676, 687-688 (Ullrich); see also FF 276, 290.

entitled to a patent." This statute has been interpreted by the Supreme Court to preclude the grant of a patent on articles or processes of nature. Gottschalk v. Benson, 409 U.S. 63, 93 (1972); Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 130-131 (1948).

Further, an interpretation of the '008 patent claims that entails coverage of the intracellular processes of host cells is incompatible with 35 U.S.C. 112 which provides:

> The specification shall contain a written description of the invention . . . in such full, clear, concise, and exact terms . . .
>
> * * *
>
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims are to be construed by reference to the patent specification, Loctite Corp. v. Ultraseal Ltd., 781 F.2d 861, 867 (Fed. Cir. 1985); Autogiro Company of America v. United States, 384 F.2d 391, 397-398 (Ct. Cl. 1967), and by reference to the language of the claims themselves, Aro Mfg. Co. v. Convertible Top Replacement Co., 365 U.S. 336, 339 (1961), W.L. Gore & Assocs., Inc. v. Garlock, Inc., 721 F.2d 1540, 1548 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). The '008 patent specification does not describe the processes that take place within the host cells, and the '008 patent claims do not particularly point out the intracellular processes. Accordingly, there is no basis in the specification or the claims themselves for the interpretation sought by Amgen.

CONCLUSION

We conclude that subject matter jurisdiction under subsection 337(a)(1)(B)(ii) may be invoked only when process patent claims exist. We further conclude that the '008 patent covers articles, i.e., host cells, but not processes. Under these circumstances, we determine that the Commission does not have subject matter jurisdiction over Amgen's complaint. Accordingly, we dismiss Amgen's complaint for lack of subject matter jurisdiction. In view of our determination, the Commission takes no position on the remainder of the ID.

VIEWS OF CHAIRMAN ANNE E. BRUNSDALE
AND VICE CHAIRMAN RONALD A. CASS

Certain Recombinant Erythropoietin
Inv. No. 337-TA-281

We concur with the Commission majority to the extent that it determines that the Complainant in this investigation is not entitled to relief. However, we are not persuaded that the Commission's dismissal on the ground that we lack subject matter jurisdiction to dispose of the investigation on the merits is the correct course of action. Instead, we believe that the Commission should issue an Order stating that, having reviewed the Initial Determination ("ID"), we affirm (with slight modifications), and, therefore, terminate the investigation on the basis that there is no violation of Section 337. We explain the reasons for our belief in these Views.

I.

This investigation originated with the filing of a complaint under Section 337 of the Tariff Act of 1930[1] on behalf of Amgen, Inc.[2] The complaint, as amended, alleged unfair practices in

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1/ Ch. 497, § 337, 46 Stat. 590, 703-04 (then codified as amended at 19 U.S.C. §§ 1337, 1337a (1982 & Supp. III 1985)).

2/ *See* Certain Recombinant Erythropoietin, Inv. No. 337-TA-281, Initial Determination at 2 (Jan. 11, 1989).

the importation into and sale in the United States of certain recombinant erythropoietin ("EPO")3/ manufactured in Japan by a process which, if practiced in the United States, would infringe certain claims of U.S. Letters Patent 4,703,008 ("the '008 patent") owned by Amgen.4/

Following institution, the Administrative Law Judge ("ALJ") conducted a thorough investigation in accordance with the statute and Commission rules. As indicated above, the ALJ concluded the investigation with an Initial Determination finding that there is no violation of Section 337 in the importation of recombinant EPO "by reason of infringement" of the '008 patent.5/ The ALJ determined, correctly we believe, that the '008 patent did not cover the process by which Respondent produces EPO. Instead, the ALJ determined, the '008 patent covers only a product (genetically engineered host cells, vectors, and DNA sequences used to make recombinant erythropoietin) and does not directly, or by implication, protect a process. Hence, the claimed process

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3/ EPO is a prescription drug administered to persons suffering from anemia associated with chronic kidney disease.

4/ ID at 2. The complaint, which was filed prior to enactment of the Omnibus Trade and Competitiveness Act of 1988, Pub. L. No. 100-418, § 1342, 102 Stat. 1107, 1212-16, also alleges, _inter alia_, that the effect or tendency of the unfair acts is to destroy or substantially injure an efficiently and economically operated industry in the United States. The Omnibus Act, however, became effective in the course of the investigation and repealed the injury test for patent-based Section 337 complaints. _Id_., § 1342(a)(1), 102 Stat. at 1212.

5/ ID at 1.

infringement was not ground for finding a violation under Section 337.

Having reviewed the ID, we would affirm it in its entirety save for a few, slight modifications that the majority apparently also has included in the Commission Opinion.6/ The one significant point of difference among Commissioners is whether the complaint should be dismissed for want of jurisdiction or, in conformity to the ID, on the merits. We believe the ALJ rightly determined that the Commission plainly has jurisdiction over this matter but, because the scope of the patent is less than was alleged by Complainant, we do not have statutory authority to grant a remedy for the actions of which Amgen complains. We believe the majority needlessly engenders confusion by styling its decision a dismissal for want of jurisdiction.

6/ First, we would supplement the ID's discussion of the scope of coverage of the patent, ID at 21-25, with citation to legal authority. Second, we would delete the incorrect statutory citation in the ID's "Conclusion of Law" number 7, ID at 71-A, and replace it with the correct citation, i.e., 19 U.S.C. § 1337(a)(3)(A). Third, we would state that the Commission does not adopt the section titled "The Commission Powers Under Section 1337", ID at 25-30, because it is not necessary to reach the matters discussed in that section to dispose of the instant investigation. In addition, we would delete the word "under" in the fourth line of Finding of Fact number 2, ID at 72, and insert in its place the following: "to determine whether there was a violation of".

For the past few years, Commission practice has been such that, once a majority of the Commission appears, Commissioners not part of that majority are denied further access to draft opinions. Since the majority in this investigation did not solidify until after circulation of the first draft opinion, our comments on the contents of the majority opinion necessarily relate to the views set forth in the first draft.

II.

Our belief that the Commission should substantially affirm the ID and dispose of the investigation by dismissing the complaint on the merits is founded on Congress's grant of jurisdiction to the Commission to conduct this investigation. As the relevant portion of the statute governing Section 337 investigations, 19 U.S.C. § 1337(b)(1), provides:

> The Commission shall investigate any alleged violation of this section on complaint under oath or upon its initiative. Upon commencing any such investigation, the Commission shall publish notice thereof in the Federal Register. The Commission shall conclude any such investigation, and make its determination under this section, at the earliest practicable time 7/

We believe that Congress' command that "[t]he Commission shall investigate any alleged violation of this section on complaint under oath" is compellingly clear. It grants the Commission the jurisdiction, at a minimum, to investigate all allegations of violations of Section 337 on complaints properly filed with the Commission. We are unable to conceive of a grant of jurisdiction that is more direct or unambiguous. We are aware of no Commission opinion or other legal authority construing this jurisdictional grant to mean something other than what the text plainly says, that the Commission's jurisdiction extends to investigation of any complaint, under oath, claiming violation of Section 337.

The only court case referenced by the majority in connection with its conclusion that the Commission lacks subject matter

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7/ 19 U.S.C. § 1337(b)(1) (emphasis added).

jurisdiction, Federal Trade Commission v. Ernstthal,8/ is not precedent for dismissal of a Section 337 complaint for want of subject matter jurisdiction. In that case, the court addressed the specific issue whether "the FTC lacks jurisdiction under § 5 of the FTC Act...to initiate [that] proceeding."9/ As the FTC Act makes clear, however, that commission initiates an adjudicatory proceeding only when it shall have "reason to believe" of the existence of an unfair method of competition and it "appears" that a proceeding would be in the public interest. The discretion accorded the FTC under its governing statute stands in sharp contrast to the imperative command of Section 337.

The general principle articulated in Ernstthal, that an agency is empowered to conclude at any point in an investigation that the "requisite jurisdictional facts are absent,"10/ is inapposite here. Clearly, the ITC, like the FTC, must terminate an investigation if the Commission properly determines that it

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8/ 607 F.2d 488 (D.C. Cir. 1979).

9/ Id. at 489-90 (citation omitted). The relevant paragraph of section 5 of the FTC Act, 15 U.S.C. § 45(b), provides:

> Whenever the Commission shall have reason to believe that any such person, partnership, or corporation has been or is using any unfair method of competition or unfair or deceptive act or practice in commerce, and if it shall appear to the Commission that a proceeding by it in respect thereof would be to the interest of the public, it shall issue and serve upon such person, partnership, or corporation a complaint stating its charges in that respect and containing a notice of a hearing . . . .

10/ 607 F.2d at 490.

lacks subject matter jurisdiction.11/ That does not, however, suggest that the requisite jurisdictional facts are absent. Here, the Commission has jurisdiction to investigate any complaint alleging a violation of Section 337. The jurisdiction that existed in this investigation when complainant alleged that its patent covered a process used by Respondents to produce products imported into the United States did not disappear when the ALJ found, or when we find, that the facts alleged by Complainant do not establish the patent infringement alleged. The ID determined that Complainant's patent covered host cells that are used solely to manufacture EPO by a recombinant process, but that this product patent did not extend to any process for using the host cells to produce EPO. Hence, the ALJ determined that the facts in evidence did not demonstrate an infringement

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11/ Otherwise, any action it takes would be ultra vires. If the Commission, for example, were to determine at any time that a Section 337 investigation it had instituted upon alleged facts cloaked in the "unfair method of competition" language characteristic of such complaints, was in fact based solely on acts within the purview of the antidumping or countervailing duty laws, the appropriate course of action in that case would be to dismiss not on the merits, but for lack of subject matter jurisdiction. See 19 U.S.C. § 1337(b)(3); S. REP. NO. 249, 96th Cong., 1st Sess. 260-61 (1979) (explaining that Congress amended § 1337(b)(3) "to require the ITC to terminate an investigation begun, or not to institute an investigation, when it has reason to believe that the matter before it is based solely on alleged acts and effects which are within the purview of the countervailing duty or antidumping duty law."); H.R. REP. NO. 317, 96th Cong., 1st Sess. 189-90 (1979) (stating that section 1105(a) of the Trade Agreements Act of 1979 "clarifies the relationship between the jurisdiction of the Commission under section 337 and the shared jurisdiction of the Secretary of the Treasury...and the Commission under the antidumping and countervailing duty laws, both of which deal with unfair trade practices"). See also Syntex Agribusiness, Inc. v. ITC, 659 F.2d 1038, 1046 (C.C.P.A. 1981) (Nies and Baldwin, JJ., concurring).

within the purview of U.S. law. If this were a basis for concluding that the Commission lacks jurisdiction, no claim would ever be dismissed on the merits; every negative decision in an investigation would be "jurisdictional." There simply is no basis in law for such a view.

The Commission majority concludes it lacks subject matter jurisdiction over a complaint alleging such activity on the ground that the Complainant did not establish a true process claim in its patent and that assertion of such a process claim is a "condition precedent" for invoking the jurisdiction of 19 U.S.C. § 337(a)(1)(B)(ii). The Complainant did, however, claim that the process used by Respondents violated the '008 patent. The statute does not predicate our jurisdiction to investigate on the ultimate decision that such allegations are both legally and factually correct. The disposition of this complaint following the ALJ's determination of no infringement cannot reasonably be thought to indicate the absence of allegations adequate to support our investigation. The Commission clearly has subject matter jurisdiction to conduct the investigation and make a determination on the merits of the complaint; it simply has no authority to grant relief once it has determined that the acts complained of do not constitute a violation of Section 337.

III.

Nothing in the legislative history of Section 337 suggests a basis for ignoring the plain meaning of the statutory text. The

intent to treat Section 337(b) as establishing the ambit of the Commission's investigatory jurisdiction is clear, as is the absence of any intent that the substantive authority defined by Section 337 can be interpreted to reduce that jurisdiction.

In the original version of Section 337, Congress' jurisdictional grant to the ITC's predecessor, the Tariff Commission, was found in subsection (b), which provided: "To assist the President in making any decisions under this section the commission is hereby authorized to investigate any alleged violation hereof on complaint under oath or upon its initiative."12/ When Congress renamed the Commission and substantially amended Section 337 in the Trade Act of 1974, it clarified the renumbered jurisdictional grant.13/ As the Senate Finance Committee explained, Congress intended that the amended and newly numbered provision

> would continue, as under present law, to authorize the Commission to investigate alleged violations of Section 337 on complaint or on the Commission's initiative . . . .
> Under amended section 337(b)(1), it is the intent of the Committee that an investigation be commenced by the Commission as soon as possible after receipt of a properly filed petition, but it is not the intent of the Committee to compel the Commission to institute an investigation before it has had an adequate opportunity to identify sources of relevant information, assure itself of the availability thereof, and, if deemed necessary, prepare subpoenas therefor, and to give attention to other preliminary matters.14/

12/ Tariff Act of 1930, ch. 497, § 337(b), 46 Stat. 703 (emphasis added).

13/ Pub. L. No. 93-618, § 341, 88 Stat. 1978, 2053-54 (1975) (codified as amended at 19 U.S.C. § 1337(b)(1)).

14/ S. REP. NO. 1298, 93d Cong., 2d Sess. 194 (1974).

An even more unequivocal statement reflecting Congress' intent that subsection 337(b) is a jurisdictional grant, as opposed to a mere filing requirement, is found in the amendments to 19 U.S.C. § 1337(b)(3) in the Trade Agreements Act of 1979.15/ As the House Committee on Ways and Means explained:

> The U.S. International Trade Commission is to investigate any alleged violation of section 337 on complaint under oath.
>
> ... Section 1105 of the bill amends section 337 in several respects. Section 1105(a) clarifies the relationship between the *jurisdiction* of the Commission under section 337 and the shared jurisdiction of the Secretary of Commerce...and the Commission under the antidumping and countervailing duty laws, both of which deal with unfair trade practices and are being extensively amended in Title I of the bill....16/

The history of the specific substantive authority at issue here does not suggest any basis for contracting the jurisdiction granted by Section 337(b). As originally enacted in 1930, Section 337 prohibited "Unfair methods of competition and unfair acts in the importation of articles into the United States."17/ Soon thereafter, the Commission defined the importation of products covered by a valid U.S. patent as an unfair act under Section 337.18/ As noted in the ID,19/ the Commission

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15/ Pub. L. No. 96-39, § 1105(a), 93 Stat. 144, 310-11 (1979).

16/ H.R. REP. NO. 317, 96th Cong., 1st Sess. 189-90 (1979) (emphasis added).

17/ Tariff Act of 1930, ch. 497, § 337(a), 46 Stat. 703.

18/ *See* In re Orion, 71 F.2d 458 (C.C.P.A. 1934).

19/ *See* ID at 11-12. Our analysis of the legislative history does not differ substantively from that of the ALJ. As noted above, we would adopt his discussion in the ID.

subsequently took the position that the statute prohibited the importation of a product produced abroad pursuant to a process patented in the United States, even though such process was not patented in the country of manufacture.20/ In Amtorg, the Court of Customs and Patent Appeals, a predecessor of our current reviewing court for Section 337 cases, reversed the Commission on the ground that the conduct complained of did not amount to patent infringement, and therefore did not constitute an unfair act within the meaning of Section 337.21/ Significantly, the court reversed the Commission on the merits, finding no violation of Section 337, and not on jurisdictional grounds.

Congress enacted Section 337a in 1940 to provide authority for a different substantive result than that in Amtorg. Section 337a expanded Section 337's definition of unfair acts to include the importation of a product manufactured according to a process covered by a valid and enforceable U.S. patent. Congress did not, in adopting this provision, suggest that the Amtorg court erred in failing to order dismissal for want of jurisdiction. Rather, the law was changed simply to provide what was missing in Amtorg, substantive authority to grant relief over

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20/ See In re Amtorg Trading Corp., 75 F.2d 826, 828 n.3 (C.C.P.A.), cert. denied, 296 U.S. 576 (1935).

21/ Id. at 831-34. Under the patent territoriality rule, which provides that patents are enforceable only in the issuing country, such conduct still did not constitute infringement under the patent law until enactment of the Process Patent Amendments Act of 1988 as part of the Omnibus Trade and Competitiveness Act of 1988. Pub. L. No. 100-418, §§ 9001-07, 102 Stat. 1107, 1563-67.

extraterritorial actions that use processes protected by valid and enforceable U.S. patents. No conceivable basis exists for reading that expansion of our authority as if it were intended to contract the scope of ITC jurisdiction that obtained when Amtorg was decided. That, however, is the effect of the majority's decision today.

IV.

For the foregoing reasons, we would affirm the ID and dismiss the complaint on the merits.

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PUBLIC VERSION

UNITED STATES INTERNATIONAL TRADE COMMISSION
Washington D.C.

In the Matter of		
	)	Investigation No. 337-TA-281
CERTAIN RECOMBINANT ERYTHROPOIETIN	)	

INITIAL DETERMINATION
Administrative Law Judge Sidney Harris

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PUBLIC VERSION

UNITED STATES INTERNATIONAL TRADE COMMISSION
Washington D.C.

In the Matter of	)	
	)	Investigation No. 337-TA-281
CERTAIN RECOMBINANT	)	
ERYTHROPOIETIN	)	
	)	

INITIAL DETERMINATION

Sidney Harris, Administrative Law Judge

Pursuant to the Notice of Investigation (53 Fed. Reg. 3947), this is the Administrative Law Judge's Initial Determination in the Matter of Certain Recombinant Erythropoietin, U.S. International Trade Commission Investigation No. 337-TA-281. 19 C.F.R. § 210.53(a).

The Administrative Law Judge hereby determines that there is no violation of § 337 of the Tariff Act of 1930, as amended, in the importation of certain recombinant erythropoietin, by reason of infringement of U.S. Letters Patent No. 4,703,008.

I. PROCEDURAL HISTORY

By publication in the Federal Register on February 10, 1988, the Commission gave notice of the institution of an investigation under section 337 of the Tariff Act of 1930, 19 U.S.C. Sec. 1337a, pursuant to a complaint filed by Amgen, Inc. ("Amgen") of Thousand Oaks, California, to determine whether there is a violation of subsection (a) of section 337 in the unlawful importation of certain recombinant erythropoietin into the United States, or in its sale, by reason of alleged manufacture abroad by a process which, if practiced in the United States, would infringe claims 2, 4-7, 23-25 or 27-29 of U.S. Letters Patent 4,703,008, the effect or tendency of which is to destroy or substantially injure an efficiently and economically operated domestic industry, and/or to prevent the establishment of such an industry in the United States. 53 Fed. Reg. 3947-3948 (February 10, 1988). The Commission named Amgen the Complainant and the following companies as respondents:

Chugai Pharmaceutical Co., Ltd.
Tokyo, Japan

Chugai U.S.A., Inc.
New York, N. Y.

Marcia H. Sundeen, Esq. and Cheri M. Taylor, Esq., Office of Unfair Import Investigations, were designated as the Commission Investigative Attorneys. 53 Fed. Reg. 3948 (February 10, 1988).

Chief Administrative Law Judge Janet D. Saxon designated Administrative Law Judge Sidney Harris to preside over this investigation.

A Preliminary Conference was held in this investigation on February 19, 1988. Appearances were made on behalf of complainant Amgen, Inc.; respondents Chugai Pharmaceutical Co., Ltd. and Chugai U.S.A., Inc.

("Chugai"); and the Commission Investigative Staff. The prehearing and hearing schedule for this investigation were set at this time. The investigation was bifurcated into separate phases concerning the patent and economic issues. Discovery regarding the economic issues was not to commence until the second phase of the investigation although if a particular discovery request sought information relevant to both the patent and economic issues, discovery was to go forward. Order No. 3 (February 23, 1988). The Administrative Law Judge issued a notice amending the hearing schedule on April 26, 1988.

On February 16, 1988, Chugai moved for summary determination. Motion Docket No. 281-1. Chugai also sought to stay discovery and the requirement that a response to the complaint and notice of investigation be filed until their summary determination motion had been ruled upon. Motion Docket No. 281-2. At the Preliminary Conference, Motion 281-2 was denied. See Order No. 3. Also, because Chugai's summary determination motion was in the nature of a motion to dismiss for failure to state a cause of action upon which relief could be granted, it was considered as such and ruled upon using standards applicable to such motions under the Federal Rules of Civil Procedure. Chugai's motion for summary determination was subsequently denied. Order No. 4 (March 7, 1987). Chugai's request that the Administrative Law Judge determine under Commission Rule 210.70(b) that interlocutory review of Order No. 4 was appropriate was also denied. Order No. 7 (April 4, 1988).

On March 22, 1988, pursuant to a joint motion of Amgen and Chugai (Motion Docket No. 281-8), the Administrative Law Judge amended the protective order in this investigation (Order No. 1, February 4, 1988) to

allow two in-house counsel of Amgen, two legal advisors for Chugai and two in-house technical experts for each party to have access to confidential information submitted by the opposing party. Order No. 5. Order No. 5 stated that the amendment granted Amgen and Chugai access only to confidential information provided by the opposing party. Order No. 5 further stated that confidential information supplied by a third party during discovery was to be designated "Third Party Confidential" could not be released to the eight individuals designated in the amended protective order without written consent of the supplier.

On March 7, 1988, The Upjohn Co. moved to intervene in the investigation (Motion Docket No. 281-7) as a party-respondent on the basis of a memorandum of intent entered into with Chugai to form a jointly-owned U.S. corporation to develop and market Chugai's product, including EPO. Because of the then-contingent nature of Upjohn's interest in this investigation and the apparent identity of Upjohn's and Chugai's ultimate objectives therein, Motion 281-7 was denied. Order No. 6 (March 31, 1988). On April 12, 1988 Upjohn requested reconsideration of Order No. 6 asserting that Upjohn's interest in the investigation was not of a contingent nature because formation of the joint venture only awaited formalization. Motion Docket No. 281-19. On April 27, 1988, the Administrative Law Judge issued an Initial Determination granting Upjohn status as a party for the economic phase of the investigation upon the formation of the joint venture corporation. Order No. 10, April 27, 1988. The corporation was formed on May 12, 1988 and Upjohn became a party upon the Commencement of the second phase of the investigation. On May 20, 1988, the Commission decided not to

review the Initial Determination in Order No. 10, 53 Fed. Reg. 20191 (June 2, 1988).

On March 11, 1988 Amgen moved to strike those affirmative defenses asserted by Chugai in paras. 12.8 and 12.11 of its response to the complaint. Motion Docket No. 281-10. Because the argument raised in these affirmative defenses were related to the economic issues in this investigation, the Administrative Law Judge deferred ruling on the motion to strike until the second phase. Order No. 13, May 10, 1988. The motion was rendered moot when Amgen's summary determination on the economic issues was granted on September 28, 1988. See Opn. at 61-72.

On March 23, 1988, Chugai moved to supplement its response to the complaint. Motion Docket No. 281-13. This motion was granted in Order No. 13, May 10, 1988.

On May 6, 1988, Chugai and its licensor, Genetics Institute Inc. ("G.I."), each sought a modification of the protective order to permit certain information in Chugai's possession which was supplied by G.I. on a confidential basis, to be designated "Third-Party Confidential" and thus be inaccessible to the in-house personnel of Amgen designated in Order No. 5. Motion Docket Nos. 281-26 and 281-27. 1/ The information in question was already in the possession of Chugai when the protective order was modified by Order No. 5. Furthermore, Amgen had already provided similar information to Chugai without restriction and it would have been unfair to deny Amgen the opportunity to examine information that Chugai had already

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1/ Because G.I. is not a party to this investigation its request was not a motion. However, it was assigned a Motion Docket number by the Secretary's Office and was treated as a motion by the parties and Administrative Law Judge.

agreed to release. Accordingly, Motions 281-26 and 281-27 were denied. Order No. 14, May 16, 1988. On May 23, 1988, G.I. applied for interlocutory review of Order No. 14. This application was denied. Order No. 17, June 10, 1988.

On May 9, 1988, Chugai moved to further amend the protective order to prevent the in-house personnel of Amgen and Chugai who were designated in the amended protective order from participating in the inspections of plant facilities. Motion Docket No. 281-28. This motion was denied. Order No. 14, May 16, 1988.

On June 8, 1988, Chugai moved to strike certain portions of Amgen's pre-hearing statement (Motion Docket No. 281-42), or in the alternative to declare the investigation more complicated. Motion Docket No. 281-43. In denying Motion 281-42, the Administrative Law Judge noted that Amgen had made clear that it was proceeding solely under then 19 U.S.C. § 1337a and contending that the '008 patent contain both product and process claims. Order No. 18, June 17, 1988. The Administrative Law Judge denied Motion 281-43 without prejudice to renewing it at a later time if the record of the phase one hearing were reopened to take further evidence. Id.

The hearing on the patent issues commenced June 20, 1988 with the testimony of Dr. Goldwasser being taken out of turn on June 17, 1988. The hearing adjourned on June 24, 1988. Motions that certain direct exhibits be received without sponsoring witnesses had been filed by Chugai (Motion Docket No. 281-44, filed June 10, 1988) and Amgen (Motion Docket No. 281-47, filed June 20, 1988) and were granted at the hearing. Chugai's motion to disqualify Amgen's expert witness, Mr. Thomas Kiley, (Motion Docket No.

281-45, filed June 14, 1988) was mooted when Amgen declined to call Mr. Kiley as a witness. Allegretti, Tr. 644.

On July 21, 1988, Chugai moved to rescind the modification of the protective order set forth in Order No. 5 Motion Docket No. 281-48. The modification had been ordered to allow counsel to take advantage of the technical expertise of the parties' in house personnel. This expertise assisted counsel in focusing the patent-based issues and in presenting them to the Administrative Law Judge. Upon the completion of the patent phase, the need for this technical expertise was obviated. Accordingly, respondents' motion was granted and the modification to the protective order was rescinded. Order No. 21, September 2, 1988.

On July 25, 1988, Amgen moved to declassify certain exhibits. Motion Docket No. 281-49. This motion is hereby granted. 2/

On August 23, 1988, the Omnibus Trade and Competitiveness Act of 1988 ("Trade Act") was enacted into law, amending 19 U.S.C. § 1337, Pub. L. 100-418 (1988). The Trade Act stated that the amendments to § 1337 contained therein applied to all pending investigations. H.R. 4848, 100th Cong., 2d. Sess. (1988) at 270. On August 23, 1988, the Commission promulgated interim rules reflecting the amendments to § 1337. These rules govern all pending § 337 investigations. 53 Fed. Reg. 33043 (August 29, 1988).

On August 3, 1988, Amgen moved to strike the affirmative defenses of inequitable conduct before the Commission and unclean hands. Motion Docket No. 281-53. These defenses were based upon an allegedly blocking patent owned by Genetic Institute (the 195 patent) and which is the subject of an

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2/ The confidential status of these documents should be preserved to allow Chugai the opportunity to appeal this decision.

infringement action in the United States District Court of Massachusetts. On a motion for summary judgement that court ruled in G.I.'s favor and found Amgen to be an infringer. However, no opinion had issued and the court had not ruled on the validity of the '195 patent. Further, Chugai's affirmative defenses were in the nature of an impermissible counterclaim (which, as general matter, are not permitted in § 337 investigation) and the alleged inequitable conduct was found not to be a permissible defense under the rule set forth in Akzo, N.V. v. U.S. International Trade Commission, 1 U.S.P.Q. 2d 1241 (1986). Accordingly, Motion 281-53 was granted. Order No. 21, September 2, 1988.

On August 15, 1988, Amgen moved for summary determination of the economic issues in this investigation. Motion Docket No. 281-55. On September 16, 1988, Chugai and Upjohn filed responses in opposition to Amgen's motion. The Commission Investigative Attorney ("Staff") filed a response in support of Motion 281-55 on September 16, 1988. On September 19, 1988, Chugai filed a motion requesting oral argument on the summary determination motion. Motion Docket No. 281-77. On September 23, 1988 the Administrative Law Judge granted motion 281-77 and ordered that oral argument on Motion 281-55 would be heard on September 28, 1988. Order No. 22, September 23, 1988. Amgen's motion was orally granted at the hearing. Tr. 1528.

On October 12, 1988, the Administrative Law Judge issued an Initial Determination designating this investigation "more complicated" and extending the date for completion of this Initial Determination. Order No. 24, October 12, 1988. On November 2, 1988, the Commission decided not to review the Initial Determination in Order No. 24.

On September 7, 1988, Amgen moved to amend the Notice of Investigation in this Investigation. Motion Docket No. 281-67. On September 20, the Commission Investigative Attorney also moved to amend the Notice of Investigation. Motion Docket No. 281-80. Amgen withdrew Motion 281-67 on September 27, 1988. Staff's proposed amendment reflected the changes in § 337 effected by the Trade Act. An Initial Determination granting Staff's motion and amending the Notice of Investigation was issued on October 21, 1988. Order No. 26. On November 16, 1988, the Commission decided not to review the Initial Determination in Order No. 26.

This Initial Determination is based on the entire record of this proceeding. Proposed findings not herein adopted, either in form or in substance, are rejected as not being supported by the evidence or as involving immaterial matters.

The findings of fact include references to supporting evidentiary items in the record. Such references are intended to serve as guides to the depositions, exhibits, and testimony supporting the findings of fact; they do not necessarily represent complete summaries of the evidence supporting each finding. Some of the findings of fact are contained only in the opinion.

The following abbreviations are used in this Initial Determination:

CX -	Complainant's Exhibit (followed by its number and the reference page(s)).
CRX -	Complainant's Rebuttal Exhibit
CPX -	Complainant's Physical Exhibit
RX -	Respondents' Exhibit
RRX -	Respondents' Rebuttal Exhibit
RPX -	Respondents' Physical Exhibit
SX -	Staff Exhibit
SRX -	Staff Rebuttal Exhibit
SPX -	Staff Physical Exhibit
FF -	Finding of Fact
Dep.	Deposition
Tr.	Transcript

II. UNFAIR PRACTICES IN IMPORT TRADE UNDER FORMER 19 U.S.C. § 1337a

A. Issues Presented

The principal issue in this investigation is whether the respondents have and are committing an unfair trade practice in the importation of erythropoietin (hereinafter "EPO"). The respondents have in effect admitted that they use host cells which are within the claims of the '008 patent in the manufacture of recombinant erythropoietin abroad. FF 502-583. Respondents claim that the use of a patented product abroad does not constitute patent infringement under 35 U.S.C. § 271 because the grant of exclusive patent rights is limited to the territory of the United States. See, Deepsouth Packing Co., Inc. v. Laitram Corp., 406 U.S. 518 (1972). However, the importation of an article manufactured abroad through the use of a process which, if practiced in the United States, would infringe a valid and unexpired U.S. patent is an unfair act under § 337 of the Tariff Act of 1930 as amended. 19 U.S.C. § 1337 (a)(1)(B)(ii). 3/ Thus, whether there is an unfair trade practice in the respondents importations of erythropoietin depends primarily on the scope of 19 U.S.C. § 1337 (a)(1)(B)(ii) and on the nature of the claims described in the '008 patent.

1. The Amtorg Trading Decision And Former 1337a

Former 19 U.S.C. § 1337a was enacted in response to the decision of the Court of Customs and Patent Appeals in In Re Amtorg Trading Corporation, 75 F.2d 826 (C.C.P.A.), cert. denied, 296 U.S. 576 (1935).

3/ Section 1337 (a)(1)(B)(ii) was enacted into law on August 23, 1988 and gives substantive effect to former § 1337a. Because the August 23, 1988 amendments did not alter the scope of former § 1337a, and because analysis of former § 1337a shows the legislative intent with greater clarity this Initial Determination often makes reference to former § 1337a instead of the current law, and for purposes of readability the word "former" in reference to former § 1337a is sometimes omitted.

The issue in that case was whether the importation of a product made abroad by a patented process constituted an unfair trade practice under § 337. The Court in a prior decision, In Re Northern Pigment Co., 71 F.2d 447 (C.C.P.A. 1934), had held that such importations constitute unfair trade practices. In Amtorg, however, the Court reversed itself, and held such importations do not constitute unfair trade practices. The Court noted that relief under 19 U.S.C. § 1337 as granted by the Tariff Commission related "solely" to the use abroad of a process patented in the U.S., and that in enacting section 1337 Congress had not sought to extend or broaden the field of substantive patent rights. 75 F.2d at 834. Because the exclusive patent grant is limited to the territory of the United States, the Court held that use of the patented process abroad did not constitute patent infringement. Id. at 831. Therefore, the importation and sale of a product made by the patented process also did not constitute infringement. [4] Since the Court decided that the existence of an unfair trade practice depended upon whether there was patent infringement, importations of the product made by the patented process abroad did not constitute an unfair trade practice. Id at 830-831.

4/ The Omnibus Trade Act of 1988 added a new subsection to 35 U.S.C. § 271 which provides that the importation into or sale or use within the United States of a product made by a patented process constitutes infringement. Subsection (g) reads in pertinent part as follows:

> Whoever without authority imports into the United States or sells or uses within the United States a product which is made by a process patented in the United States shall be liable as an infringer, if the importation, sale, or use of the product occurs during the term of such process patent.
>
> Omnibus Trade and Competitiveness Act of 1988, Pub. L. 100-418, § 9003 (1988)

In response to the Amtorg decision Congress eventually provided legislative relief in the form of 19 U.S.C. § 1337a. Section 1337a read as follows:

> The importation for use, sale, or exchange of a product made, produced, processed, or mined under or by means of a process covered by the claims of any unexpired valid United States letters patent, shall have the same status for the purposes of section 1337 of this title as the importation of any product or article covered by the claims of any unexpired valid United States letters patent.
>
> former 19 U.S.C. § 1337a

2. Statutory Interpretation Of Former § 1337a

Complainant makes several arguments concerning the appropriate interpretation of the statute. It argues that the statute's reference to "any patent" means that relief under § 1337a does not require that the patent claims at issue be traditional process claims to invoke the jurisdiction of the statute. Complainant further argues that § 1337a is a statute of broad applicability, and is to be construed as making unlawful the importation of a product made by a process "covered by" claims other than traditionally worded process claims. Amgen further asserts that the claims at issue are "hybrid" in that they cover not only the DNA sequence, vectors and host cells, but also those intracellular processes, inseparable from the cell, that are utilized by the cell to manufacture EPO. Thus, Amgen concludes, Chugai's use of the patented host cells to make EPO constitutes the use of processes "covered by" the claims of the '008 patent and the importation of Chugai's EPO is an unfair trade practice under § 1337a.

A proper analysis of former § 1337a begins with the statute's language. Two clauses make up § 1337a. The first or active clause, which

defines the addition to the law made by the then new enactment, when read by itself is ambiguous, but is clarified when contrasted against the second clause. The first clause when viewed apart from the second, may be simplified as follows: "The importation ... of a product made ... by means of a process covered by the claims of any unexpired valid United States letters patent ... ." If the statute contained a comma after the word "process" it would be clearer that the process was what was "covered by the claims" of the valid, unexpired patent. Without the comma, one could argue that "covered by the claims" refers to "a product made ... by means of a process." By this interpretation, since every product is made by a process of some sort, the word "process" in clause one is unimportant and close to surplusage. Continuing along this line, the clause may be further simplified as follows: The importation of a "product" "covered by the claims" of "any" unexpired valid United States letters patent. In this context the phrase, "covered by the claims of any valid patent," appears to give very broad scope to the statute. "Any" patent means just that, and "covered by the claims" in conjunction with the term "any" patent appears to justify inclusion of product as well as process claims within the clause.

Analysis of the second clause clarifies the meaning of the first clause and thus of the legislation. The second clause merely states that the importations included in the first clause shall have the same status under § 1337 "as the importation of any product or article" covered by the claims of an unexpired valid U.S. patent. Obviously, clause one cannot be identical to or overlap section 1337, since in that case § 1337a would duplicate or not add anything to § 1337. Yet, interpreting the first

clause of § 1337a to mean that it refers to a product covered by the claims, as discussed above, would in effect, or in substance, lead to an interpretation that the first clause duplicates what is contained in § 1337.

Therefore, the word "process" in the first clause must be read so that the term "covered by the claims" modifies "a process," rather than an imported product. This is the only interpretation which is logical in view of the Amtorg decision, which gave rise to the need for a legislative remedy. The legislative history also clearly supports this view. Thus, relief before this Commission was available under former § 1337a and is now available under 19 U.S.C. § 1337 (a)(1)(B)(ii) when the accused import is made by means of a process, which is "covered by the claims" of a valid unexpired U.S. patent.

There has also been much discussion concerning the meaning of the term "covered by the claims." This term is not used elsewhere in the patent laws. However, the plain meaning of this term is virtually identical in substance to the term "claim construction" which has a well defined meaning in the patent laws. The plain meaning of the term "covered by the claims" refers to matters within the coverage or penumbra of the claims at issue. The term "claim construction" has been used by the courts to refer to the determination of the scope of the claims. See, McGill, Inc. v. John Zink Co., 221 U.S.P.Q. 944, 948-951. ("claim construction" used to describe the court's function of determining the scope of the claims). Thus, the phrase "covered by the claims" as used in the statute refers to the fact that properly construed claims must include a process utilized in making the imported product, to invoke the jurisdiction of the statute.

Complainant argues that although the term "process patent" was used frequently in the _Amtorg_ decision, it does not appear in section 1337a. However, prior to the enactment of 1337a the terms "process patent" or "process claim" do not seem to have been used in the patent code. A subsection of the infringement statute, 35 U.S.C. 271(c), dealing with contributory infringement does _now_ use the term "patented process"; however, this subsection's codification of the decisional law on contributory infringement was added to the patent statues by the Patent Act of 1952, some twelve years after 1337a was enacted. _See_, 4 Chisum, _Patents_ § 17.02[6]. The statutory section on the effect of a reissued patent, 35 U.S.C. § 252 (second paragraph, second sentence) similarly _now_ contains the term "process patented" and similarly contains a new codification of the judicial doctrine of intervening rights added by the Patent Act of 1952. _See_, 3 Chisum, _Patents_ § 15.02; 35 U.S.C.A. § 252 [Historical and Revision Notes]. When section 1337a was drafted, the patent statute did _not_ contain the compound terms "process claim", "process patent", or "patented process." Therefore, the absence of such terms from 1337a is not indicative in itself of any Congressional intent that the statute apply to both process and non-process patents.

The current patent statute provides that "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof," is patentable. 35 U.S.C. § 101. Current section 100(b) of Title 35 defines "process" to mean "process, art or method, and includes a new use of a known process, machine, manufacture, composition of matter of material." Prior to 1952 the patent code did not contain the term "process" in reference to patentable subject matter, but referred to

the term "art"; the prior statute made patentable "any new and useful art, machine, manufacture, composition of matter, or any new and useful improvement thereof." R.S. section 4886; 6 Chisum, Patents Appendix 14, section 24. However, no substantive change in the law was intended by the Patent Act of 1952's substitution of the term "process" for the term "art", as the term "art" had been interpreted by the courts to be practically synonymous with process or method. Senate Rep. No. 1979, 82nd Cong., 2nd Sess. (1952) [Report on Revision of Title 35], 6 Chisum, Patents Appendix 19 at 19-7, 19-22.

In the various forms of the proposed legislation 5/ which led to former 19 U.S.C. § 1337a, no mention was made of providing protection to patented products used abroad to make imported articles. Further, no mention was made in the legislative history of providing protection other than to patented processes 6/ and ample mention was made of the term "process patent" in the Congressional hearings and House and Senate Reports on H.R. 8285, and its predecessor bills which led to enactment of 1337a. The sponsor of H.R. 8285 was Rep. Peterson of Florida who testified about a

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5/ A more comprehensive statement of the legislative history of § 1337a is summarized in Appendix A attached to this Initial Determination.

6/ As introduced in the 76th Congress, Rep. Peterson's original H.R. 8285 extended to "minerals mined ... by use of the flotation process" and the bill did not initially mention patents. However, the House Committee on Mines and Mining Report by Rep. Peterson stated that the particular shipment involved in the Amtorg case "was by use of the so-called flotation process which is an American process, patented." H. Rep. No. 1781 at 3. This indicates the bill's initial orientation to patented processes. An amendment of the bill was recommended in this same Committee and in this same Committee report to cover "minerals mined, produced, or processed by use of any mining process covered by the claims of any ... patent," H.R. 8285 was amended on the floor of the House, with Rep. Peterson's approval, to expand the bill's coverage beyond minerals, and generally cover "any article, mineral, or product produced ... by use of any process covered by the claims of any ... patent."

predecessor bill in hearings before a Subcommittee of the House Committee on Patents. 7/ Congressman Peterson, in response to a direct question on what would be protected by the predecessor bill H.R. 7851, stated that:

> "This bill would protect any industry wherein foreign countries have violated a process patent. In other words, it might be a process affecting matters other than phosphate."

Hearings on H.R. 7851, 75th Cong., 3rd Sess. (1938) at 5.

This language is a plain statement of the bill's sponsor that the intended scope and extent of coverage under former § 1337a is limited to process patents. Similarly, the House Report describes the scope of this predecessor bill as follows: "H.R. 7851. . .was designed to cover all American process patents." House Report at 2. (emphasis added)

The legislative history indicates that the intent of former § 1337a was to provide protection under § 337 to a patented process equivalent to that already enjoyed by product patents. It appears that Congress, in enacting 1337a, intended to increase the protection afforded to process patents and in this statute had no intent to increase the rights afforded to product patents which were seen as already protected. As noted above, the very language of 1337a expressly provides this equivalence by stating that the importation of a product made by means of a process covered by the claims of any patent "shall have the same status for the purposes of section 337" (emphasis added) as the importation of any product or article covered by the claims of any product patent. Congressman Peterson, the bill's sponsor, testified in the Subcommittee Hearing stating the intent to

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7/ The Subcommittee was designated the Subcommittee on Phosphate Rock Process Patents, presumably because the process patent in issue in Amtorg claimed a process for refining phosphate rock. See 75 F.2d at 827.

make process patent protection equivalent to existing product patent coverage:

> Of course the chairman [of the Subcommittee] by reason of his long experience on this committee and close study, is far more familiar with the distinctions between process patents and product patents than I am; but the distinction was made, of course, [that] there is protection on product patents, but that protection does not seem to exist where a process is stolen in a foreign country and comes into this country, and the Amtorg case went off on that.

Hearings on H.R. 7851, 75th Cong., 3d Sess. (1938) at 39

The Senate Report on H.R. 8285 also expressly states an intention to make process patent protection equivalent to existing product patent protection:

> Since the Amtorg decision owners of American process patent [sic] are helpless to prevent the infringement abroad of their patent rights. This bill will give to them the same rights which the owners of product patents have.

Senate Report No. 1903, 76th Cong., 3rd Sess. (1940) at 4.

The decision in Amtorg supports this intent of providing equivalent protection to process patents, since the court there reasoned that process patents are not protected against others' sale of a product made by use of the process abroad. See, Amtorg, 75 F.2d at 832-834.

The House and Senate Reports both plainly indicate their intent to displace the rule laid down in Amtorg that the importation of products made by patented processes is not an unfair act. Again, while neither report uses the wording that a process patent is required for protection under the bill, nevertheless both Reports plainly identify the entire intended scope and purpose of the bill, which appears to be limited to process patent protection. The House Report states:

This bill is designed to correct the present problem which was created when the Court of Customs of and Patent Appeals in the case _In Re Amtorg Trading Corporation_ reversed its former decisions and held that the importation of products made abroad in accordance with a United States process patent without consent of patentee was not regarded as an unfair method of competition. The situation created by the _Amtorg_ case was recognized by the ...Tariff Commission in its annual report to Congress in 1935, stating:

> The situation created by this final decision of the court is one that requires the consideration of Congress. The owner of a process patent issued in the United States has now no protection of any kind against the use of that patented process without his consent outside the United States, and importation into and sale within the United States of goods made by the process. The patentee may not proceed against the user of the process because the patent grant of exclusive rights to use the patented process does not extend beyond the limits of the United States; he may not proceed against the importer of goods made by the process because, under the existing patent law, his sole right is against the user of the process; and no proceeding may now be started under section 337, because the importation for sale or use of articles made abroad by a process patented in the united States is not an unfair method of competition.

House Report at 1-2.

The Senate Report similarly states:

> This bill is designed to correct the present problem which was created when the Court of Customs and Patent Appeals in the case _In re Amtorg Trading Corporation_ reversed its former decisions and held that the importation of products made abroad in accordance with a United States process patent without consent of patentee was not regarded as an unfair method of competition.

Senate Report No. 1903, 76th Cong., 3rd Sess. (1940) at 1-2.

The Senate Report even more specifically describes 1337a's intent only to return the law's protection previously enjoyed by process patents withdrawn by _Amtorg_.

In short, relief under 19 U.S.C. § 1337 (a)(1)(B)(ii) is available only when the patent claims cover a process.

3. Scope of Coverage of the '008 Patent's Claims

In light of the above discussion, whether Amgen is entitled to relief under former § 1337a (and its successor provision § 1337 (a)(1)(B)(ii)), is dependent upon whether the claims of the '008 patent cover a process. Complainant contends that certain intra-cellular processes which occur in connection with the manufacture of EPO by transfected host cells are described within the claims of the '008 patent, that these processes are utilized by respondents in the manufacture of recombinant EPO abroad, and that therefore such importations constitute an unfair trade practice under former 19 U.S.C. § 1337a.

All parties agree that the claims of the '008 patent include DNA sequences encoding for human erythropoietin (Claim 2) 8/ FF 243, plasmids or vectors including the EPO DNA sequence (Claim 5) FF 253, and host cells transfected with a DNA sequence "in a manner allowing the host cell to express erythropoietin." (claim 4) CX-1. The dispute revolves around claim 4, and other similar claims, such as e.g., claim 23. Grammatically, these claims are phrased as host cells, or as article claims. However, the essential feature of these host cell claims is that they are transfected with a DNA sequence in a manner allowing the cell to express EPO. FF 246-251. Although these claims describe articles or products the description of the product is stated functionally, i.e., if the host cell is

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8/ Claim citations refer to illustrative claims and are not intended to be comprehensive.

transfected with the DNA sequence so that it produces EPO, then we know it is the article or product claimed.

Complainant argues that the host cell is merely a membrane or bag of intra-cellular processes which is utilized in the manufacture of EPO. Lin, Tr. 405; Complainant's Post-Hearing Memorandum at 10. Complainant asserts that the host cell cannot function to produce EPO without the intra-cellular processes, and that the processes are the essence of or an essential part of the cell, which cannot exist without them. Complainant's Post-Hearing Memorandum at 10-12. Complainant further argues that the host cell claims are unique hybrid claims containing both product and processes. Complainant's Post-Hearing Memorandum at 18-21. According to the complainant, this uniqueness stems from the fact that the host cells are living things, created by the new developments in the yet emerging biotechnology industry. Complainant's Post-Hearing Memorandum at 10. The host cell is not useful unless it is transfected with the proper DNA sequence in a manner which allows the cell to express EPO. FF 213, 220-221, 579-583. The cell cannot express EPO without the functioning of the intra-cellular processes. FF 191, 201-202. Such intra-cellular processes are acknowledged to exist by the experts of both parties. Goldwasser, Tr. 37-38; Ullrich, Tr. 676-677; Sadler, Tr. 859-860.

Amgen acknowledges that the U.S. Patent and Trademark Office ("PTO") refused to award traditional process claims which were contained in the Amgen application on the authority of In re Durden, 226 U.S.P.Q. 359 (Fed. Cir. 1985). Complainant's Post-Hearing Memorandum at 20-21. The Durden opinion is interpreted by the PTO to mean that a patent on an old process will not be awarded even if the starting materials are novel and the

results also yield a novel product. Complainant admits that those claims were cancelled. 9/

Complainant attempts to distinguish the processes in the cancelled claims from those it asserts are covered by the claims that were issued. It characterizes the cancelled claims as describing "extra-cellular" processes such as the growing of the cells and the use of them to produce EPO. Complainant's Posthearing Memorandum, 20-21. Complainant argues that the claims that did issue are "hybrid" in that they cover both a product (the host cells) and the intracellular processes that are inherent in the product (which synthesize EPO). Complainant's Posthearing Memorandum, 18-20.

However, the patent office history of the '008 patent does not support complainant's contention. In its application, Amgen sought to claim a process for the production of EPO that comprised the growth of transformed or transfected host cells and the isolation of the EPO produced by the host cells. CX-2, 107, 141; FF 306-312, 315. The examiner rejected these process claims (claims 69-72) under 35 U.S.C. §§ 102 and 103 in light of the prior art that discloses expressing mammalian proteins using recombinant DNA-transformed host cell microorganisms. CX-2, 334; FF 313, 317-321. The examiner also based his § 103 rejection on the grounds that the claims sought by Amgen were for the application of an old process to new materials, citing In re Durden, 226 U.S.P.Q. 359 (Fed. Cir. 1985). FF 318, 320-321. The examiner further ruled that the prior art anticipated the expression of a mammalian protein using recombinant DNA-transformed

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9/ The claims were cancelled without traverse and Amgen specifically stated it was reserving the right to pursue claims of the same or similar scope in a duly filed continuing application. CX-2 at 346.

microorganisms and therefore rejected the process claims under 35 U.S.C. § 102(b). FF 317-319.

Subsequent to these rejections, Amgen amended its application, cancelling all previously submitted claims and submitting new ones. CX-2, 341; FF 322. The amended application included a chart correlating the old claims with the new ones and stated that there were no new claims corresponding to the rejected process claims 69-72, thus mooting the rejection of the application because it contained these claims. CX-2, 346, 367; FF 324. Further, the amended application explicitly described the remaining claims as directed to DNA sequences, DNA vectors, transformed and transfected host cells. CX-2, 347; FF 323. Unlike the descriptions of the claimed subject matter submitted earlier during the application process, the amended application does not describe the claims as being directed to any process whatsoever. Compare, CX-2 at 347 with CX-2 at 180 and 239. Amgen did not attempt to resurrect its process claims in the application that ripened into the '008 patent. FF 322.

The process of growing a transfected host cell and isolating the polypeptide must necessarily include all intracellular processes, because such processes are inherent in a living organism. Sadler, Tr. 860. Amgen's expert, Dr. T. Randolph Wall, testified that the intracellular processes Amgen seeks to have covered by its claims take place as a result of the growing of the host cells under suitable nutrient conditions. Wall, Tr. 635-639. FF 569-579. The cancellation of the claims to the growth of a transfected host cell and the isolation of the polypeptide products of the expression of the DNA sequences therefore forecloses Amgen from asserting that claims to the intracellular processes were preserved in the

issued claims. Graham v. John Deere, 383 U.S. 33 (1966); Arco Industries v. Chemicast, 208 U.S.P.Q. 190, 194 (6th Cir. 1980). Further, Amgen's explicit characterization of the claims remaining in its application as being directed to products compels a conclusion that the claims of the '008 patent do not cover a process.

In addition to the prosecution history, the testimony of the inventor, Dr. Lin, rebuts Amgen's argument that the claims of the '008 patent cover the host cell's intracellular processes for making EPO. Dr. Lin was unable to indicate where the claims or specification of his own patent indicated that he was claiming the intracellular processes. Lin, Tr. 406-409. Dr. Lin also testified that he did not consider the intracellular processes to be part of his invention. Lin, Tr. 410.

In light of the nature of the claims Amgen gave up during the prosecution of the '008 patent's application, its own description of the remaining claims, and Dr. Lin's testimony as to what he considered to be his inventive contribution, the argument that the remaining claims cover intracellular processes is not persuasive. In these circumstances there seems little basis to conclude that a claim drawn to a transfected host cell together with functional language which recites that the transfection shall be in a manner allowing the cell to express EPO must or should be construed as a process claim covering the intracellular host cell processes. See FF 240-284.

B. The Commission's Powers under section 337.

In asserting that Amgen should be denied relief in this investigation, Chugai argues in effect that in a patent-based investigation, section 337

is strictly limited to the metes and bounds of the patent law, and that the enactment of section 337 gave the Commission no power to find an unfair trade practice without finding patent infringement. Such a view is in total contradiction to a long series of Supreme Court decisions interpreting the terms "unfair trade practice" and "unfair method of competition" in connection with the Federal Trade Commission Act. Further, there is nothing in the Amtorg decision or the Lannom 10/ decision cited by Chugai which would support this view.

The majority decision in Amtorg was based upon a limited view of the scope of the term "unfair" act or practice. ("They are clearly inapplicable to practices never heretofore regarded as opposed to good morals because characterized by deception, bad faith, fraud, or oppression, or as against public policy because of their dangerous tendency unduly to hinder competition or create monopoly." Amtorg 75 F.2d at 830-831. However, it is clear from FTC v. Indiana Federation of Dentists, 476 U.S. 447 (1988), among other Supreme Court decisions, that such a limitation upon the term "unfair" practice, is improper. The Amtorg court also stated that in enacting section 337 and its predecessor, Congress did not intend to enlarge substantive patent rights. Amtorg 75 F.2d at 834. However, this is merely a second or backhand way of stating that the term "unfair"

10/ In Lannom Manufacturing, Inc. v. U.S. International Trade Commission, 231 U.S.P.Q. 32 (Fed. Cir. 1986) the Federal Circuit held that where no party challenges the validity of a patent, the Commission does not have the power to disregard the presumption of validity in 35 U.S.C. § 282, and require the complainant to prove a prima facie case of validity. 231 U.S.P.Q. at 38. However the underlying premise of this decision is that the Commission investigation of an unfair trade practice was based upon patent infringement.

practices is limited by the patent laws, a proposition for which there is no authority or support.

From its inception, the purpose of section 337 has been to provide relief to United States industries from unfair acts by goods manufactured abroad. Lannom, 231 U.S.P.Q. at 38. The Supreme Court has made clear in connection with the Federal Trade Commission Act, after which section 337 was patterned, that the Commission has power to define unfair acts or practices, subject to judicial review, and that the words "unfair method of competition" may include acts which have never been specifically declared by the courts to be unfair. Amtorg, 75 F.2d at 830-831. See also, FTC v. Indiana Federation of Dentists, 476 U.S. at 454. In Dentists the Supreme Court stated:

> "The standard of 'unfairness' under the FTC Act is by necessity an elusive one, encompassing not only practices that violate the Sherman Act and the other antitrust laws [citations omitted] but also practices that the Commission determines are against public policy, for other reasons [citations omitted]. Once the Commission has chosen a particular legal rationale for holding a practice to be unfair, however, familiar principles of administrative law dictate that its decision must stand or fall on that basis, and a reviewing court may not consider other reasons why the practice might be deemed unfair."

Id. at 454-455.

By contrast, the instant investigation was instituted on a narrower basis, limited to whether the respondent's importations were in violation of section 337 by reason of application of former section 1337a. 53 Fed. Reg. 3947 (February 10, 1988). Even in a patent based case, the Commission could find an unfair trade practice in conduct short of infringement. 11/

11/ The fact that a respondent may assert all legal and equitable defenses to a complaint does not require that a patent-based case be grounded on patent-infringement. This provision merely makes available to a respondent whatever legal and equitable defenses exist to the allegations made.

There are a number of facts and circumstances established in the record which could justify a broader based investigation. First, it is clear that Chugai entered into a licensing agreement with Genetics Institute knowing that Amgen had both cloned the gene first and applied for a patent first. FF 20-22, 56. Respondents and the collaborator Genetics Institute were aware of potential patent problems which might hinder their joint venture, and sought to escape from U.S. laws by manufacturing recombinant EPO abroad. FF 41, 57. Respondents removed transfected host cells from the United States prior to issuance of Amgen's patent to use abroad to produce recombinant EPO with the intent of importing it into the United States. FF 44, 62, 66, 67.

Second, the only reason that § 1337a is not applicable to the respondent's importations of EPO is the policy of the Patent and Trademark Office, because of its interpretation of In re Durden, 226 U.S.P.Q. 359 (Fed. Cir. 1985), not to grant patents on known manipulations or methods, even though novel starting materials are used, and novel end products result. The policy expressed in In Re Durden has been subject to great controversy within the PTO and in the courts. The holding in Ex Parte MacAdams, 206 U.S.P.Q. 445 (P.T.O. Bd. App., 1978), appears to be directly contrary to the holding of Durden. That case held that it is not proper to determine the patentability of a process solely on the lack of novelty of the physical manipulative steps. The specific nature of the material employed in the process bears upon patentability of the process and if its use in the process is not obvious from the art or is responsible for unexpected results, the method as a whole must be considered unobvious. Ex Parte MacAdams at 448. The Court in Durden noted that the Board of Appeals

in Durden stated as follows: "To the extent that this decision is in any way inconsistent with the published Board of Appeals decisions in Ex parte MacAdams, 206 U.S.P.Q. 445, and Ex parte Klioze, 220 U.S.P.Q. 91 (1983), those decisions are hereby overruled." The issue which is addressed in Durden is whether a process is obvious, when a conventional method is applied to new starting materials and yields new end products. But as the Durden decision itself shows, the conclusion of obviousness in such an instance is far from clear, so that the Court declined expressly to set forth a general rule, and emphasized that it would decide each such case on the particular facts involved.

> "[T]he question of obviousness under § 103 arises in such an unpredictable variety of ways and in such different forms that [stating a general rule] would be an indiscreet thing to do. Today's rule would likely be regretted in tomorrow's case. Our function is to apply, in each case, § 103 as written to the facts of disputed issues, not to generalize or make rules for other cases which are unforeseeable.
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> 226 U.S.P.Q. 359 at 362

The application of the rule of In Re Durden to Amgen's application should be seen as in the nature of patent office policy. Such policy has been different in the past, and could change again tomorrow. Moreover, it is a policy that has been adopted by the PTO, an agency that has no responsibility in the area of international trade. The Commission and not the PTO is responsible under section 337, for the protection of American industry from unfair acts and practices in the importation of goods. The policy expressed in In Re Durden, and the resultant consequences for complainant's patent application, has determined that complainant would not receive a process patent, and that therefore it would not come within former and amended section 1337a. However, in reaching this result, the

underlying purpose of section 337, which is to protect United states industry from unfair practices involved in imported goods manufactured abroad is ignored. Permitting the decision concerning whether there is an unfair act or practice involved in respondents' importations of EPO to be decided on the PTO's view of In Re Durden, is to leave these international trade questions in the hands of the PTO. This was and is not the intent o: Congress. Since the biotechnology industry is newly emerging, (See FF 4-7 100, 108) and is an important industry for the United States, the Commission may wish to reinstitute this investigation on a different basis and determine whether there are unfair trade practices involved in respondents importation of EPO, which may fall short of or not involve patent infringement.

III. PATENT VALIDITY

A. The '008 Patent Is Not Invalid For Obviousness

Under 35 U.S.C. § 103, a patent may not be obtained if the claimed invention would have been obvious over the prior art. Section 103 provide: as follows:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

In Graham v. John Deere Co., 383 U.S. 1 (1966), the Supreme Court set forth the proper approach for an obviousness analysis:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the

> level of ordinary skill in the pertinent art resolved. ... Such secondary considerations as commercial success, long felt but unresolved needs, failure of others, etc. might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

In determining obviousness, it is not the differences between the claimed invention and the prior art that are in question, but rather it is the consideration of those differences in determining whether the claimed invention as a whole would have been obvious to one of ordinary skill in the art. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81 (Fed. Cir. 1986); Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530. (Fed. Cir. 1983). The determination requires cognizance of the invention's properties and the problem which it solves, viewed in light of the teachings of the prior art. In re Wright, 6 U.S.P.Q. 2d 1959 (Fed. Cir. 1988). It is done entirely with reference to a hypothetical person of ordinary skill in the art. This hypothetical person is presumed to have been aware of all arts reasonably pertinent to the particular problem confronting the actual inventor at the time. Pentec, Inc. v. Graphic Controls Corp., 227 U.S.P.Q. 766 (Fed. Cir. 1985). Such a person is also presumed to be aware of all the pertinent prior art but does not undertake to innovate. Standard Oil Co. v. American Cyanamid Co., 227 U.S.P.Q. 293 (Fed. Cir. 1985). In determining the level of ordinary skill, factors such as the content of the prior art, the type of problems encountered in the art, and the educational background of those active in the field are considered. See Orthopedic Equipment Co., Inc. v. United States, 702 F.2d 1005 (Fed. Cir. 1983). Considerations such as commercial success, copying, long felt need, and failure of others are an integral part of the obviousness/nonobviousness inquiry. Simmons Fastener Corp. v. Illinois

Tool Works, 739 F.2d 1473 (Fed. Cir. 1984), cert. denied, 471 U.S. 1065 (1985).

A patent shall be presumed valid. 35 U.S.C. § 282. The party asserting invalidity must therefore prove it by clear and convincing evidence. Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc., 230 U.S.P.Q. 416 (Fed. Cir. 1986). Thus, Chugai must bear the burden of proving that the '008 patent would have been obvious.

1. Scope and Content of the Prior Art

The question of obviousness must be resolved with reference to the prior art at the time the invention was made. 35 U.S.C. § 103. The prior art sources most often relied upon in an obviousness analysis are those set forth in 35 U.S.C. § 102(a) - prior knowledge or use, prior patents, and prior publications. Hercules, Inc. v. Exxon Corp., 207 U.S.P.Q. 1088 (D. Del. 1980) ("Since Section 103 does not define the term 'prior art,' courts generally look to 35 U.S.C. § 102, which defines prior art for purposes of judging novelty, as opposed to obviousness." 207 U.S.P.Q. at 1095).

It is settled law that the scope of the prior art is best defined in terms of the nature of the problem to be solved. Orthopedic Equipment Co., Inc. v. United States, 702 F.2d 1005 (Fed. Cir. 1983). However, the scientific and technical complexity of genetic engineering defy a simple description of the problem facing scientists working towards the goal of cloning the gene that encodes for erythropoietin.

A gene is a particular sequence of deoxyribonucleic acid (DNA) molecules. The subunits of DNA are called nucleotides (or bases), of which there are four - adenine, guanine, cytosine and thymine (abbreviated

respectively as "A", "G", "C" and "T"). Goldwasser, Tr. 20; FF 118. The bases occur along each of the two strands of the now-famous double helix which makes up DNA molecules. A base on one strand is always paired with its complement on the other strand: A is always paired with T, and C with G; FF 119. These bases, taken three at a time along a strand in blocks called "codons", provide a code for establishing the identification of an amino acid. Goldwasser, Tr. 20; FF 120.

Amino acids are small molecules characterized by a certain composition and a certain bond. FF 116. There are twenty amino acids which form the "building blocks" of all proteins. Sadler, Tr. 763; CPX 9, p.3; FF 116. A protein (e.g. erythropoietin) consists of a linked sequence of amino acids. Sadler, Tr. 763; FF 122. Each protein has an amino acid sequence which is characteristic to it. Sadler, Tr. 763. The structure of all proteins in cells is derived from the information encoded in the gene (or "DNA sequence") for that protein. Goldwasser, Tr. 19-20; FF 121, 123. The gene is located in the cell's nucleus and instructs the cell to make a protein of a particular composition. Thus, the gene for EPO is essentially the set of instructions in the cell telling it how to make EPO. Goldwasser, Tr. 19-20.

In general terms, the cell undertakes the following steps when it produces a particular protein. First, the complementary strands of DNA unzip, or separate. The sequence of nucleotides on one strand of the DNA is "read" by the transcription enzymes of the cell and transcribed into the

DNA's ribonucleic acid (RNA) complement known as messenger RNA. 12/ Sadler, Tr. 776; RX-89; FF 125-129.

The messenger RNA "transcript" moves out of the cell's nucleus into its cytoplasm 13/ and to one of its ribosomes where protein synthesis occurs. FF 130, 133, 140. The ribosome first finds a specific codon on the RNA molecule called an initiator codon. Sadler, Tr. 772; FF 138. In mammals, the initiator codon for all proteins made in the cytoplasm of cells is comprised of the nucleotides A-U-G which specify the amino acid called methionine. Sadler, Tr. 778-779. The ribosome then "reads" the code of the RNA molecule in a series of codons, each of which specifies a singe amino acid. FF 133, 138. The ribosome assembles a sequence of amino acids based upon the code in the RNA molecule. FF 137-138. The order of codons along the RNA determines the sequence of amino acids that are joined to make a protein. FF 133, 137-138. The conversion of each nucleic acid on the RNA into its specified amino acid is called translation. Sadler, Tr. 772-773; FF 139.

The translation process is mediated by a special type of RNA called "transfer RNA" (tRNA). Sadler, Tr. 779; FF 139. A tRNA molecule contains one region called the anti-codon, which is complementary to a specific codon along the mRNA strand that is being read. Another region of the tRNA contains the amino acid that corresponds to that specific codon. Sadler,

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12/ RNA, like DNA, is composed of nucleotides. The "T" nucleotide of DNA is replaced by a "U" nucleotide (uracil) in RNA. Thus, RNA is composed of "C", "G", "A" and "U" nucleotides. Sadler, Tr. 776-777; CX-1, col. 1, ln. 45-47; FF 129.

13/ The cytoplasm is that portion of the cell's protoplasm, or living matter, that is outside the cell's nucleus. American Heritage Dictionary (2d Coll. Ed.) 361, 996-997.

Tr. 779, RX-90; FF 139. As each amino acid is synthesized in sequence, it is attached to the growing chain of amino acids in the order specified by the codons. FF 139; See RX-90. This linking of amino acids continues until the cell's machinery encounters a stop codon which tells the protein synthesis machinery to stop. Sadler, Tr. 787-788; FF 134.

Because there are four possible nucleotides in RNA (C, G, A, and U), there are 64 possible codons or triplet combinations (4x4x4=64). Sadler, Tr. 778; FF 134. Therefore, because there are only 20 amino acids, some amino acids are encoded by more than one codon. Id. This is referred to as redundancy or degeneracy in the genetic code. Id.

After the translation process is completed, the chain of amino acids, or polypeptide is translocated across the cell and carbohydrates are added to it by a process called glycosylation. Sadler, Tr. 781-784; FF 150. Glycosylation occurs in a compartment in the cell's cytoplasm called the endoplasmic reticulum. Sadler, Tr. 781-784, 789; RPX-2; FF 150. Another post-translation process is the folding of the protein into a three-dimensional shape that is characteristic of it. FF 144. Without the specific three-dimensional shape conferred by folding, the molecule would not have a biological effect. FF 145. Finally, if necessary, the cell secretes the finished protein. Sadler, Tr. 784-785; RX-92; FF 149-151.

Dr. Lin, the inventor of the '008 patent, joined Amgen in 1981 and was assigned the project of cloning the EPO gene. Lin, Tr. 234; FF 100, 330. The goal of this research was to clone the EPO gene and put it into host cells which would express a large amount of the EPO material for clinical research. Lin, Tr. 235; FF 337. The term "cloning" refers to the act of isolating and purifying th. .A sequence, or gene, encoding for EPO and

using in vitro recombination techniques to insert the sequence into a vector. Exhibit C to Complainant's Prehearing Statement. 14/ A vector is a general term applied to a DNA molecule into which fragments of exogenous DNA may be inserted. An "expression vector" is a cloning vector designed so that a coding sequence inserted at a particular site in the molecule will be transcribed and translated into protein. Id. The vector thus functions as a "carrier" of the inserted DNA fragment. Id. It is used to transport this sequence to a host organism, such as a mammalian cell in culture, and introduce the gene into it. CX-1, col. 2, lines 21-27. In the early 1980s, the methods available for transporting an expression vector included crystals of calcium phosphate which would absorb the DNA onto themselves. Sadler, Tr. 789. These crystals containing DNA are taken up by some of the cells and under favorable conditions the host cells that take up the crystals will be transfected, i.e., the DNA will end up in the host cell's nucleus, and incorporated into its genetic material, or "genome" 15/. Sadler, Tr. 789-790. After the host cell incorporates the exogenous DNA, the existing machinery for gene expression in the transfected host cell then operates to construct the desired product, using the exogenous DNA. 16/ CX-1, col. 2, lines 27-30.

14/ Exhibit C to Amgen's Prehearing Statement is a glossary of terms used in the field of biotechnology. The glossary was not offered as an exhibit at the hearing. However, neither the Staff nor Chugai have indicated any objection to its submission. The definitions contained therein are supported by the record. The Administrative Law Judge has cited it in the interest of greater clarity.

15/ The genome it the complete set of chromosomes found in a cell. American Heritage Dictionary (2d College Ed.) 553.

16/ The desired product is also a chain of amino acids and is therefore often referred to as a polypeptide. Exhibit C, Complainant's Prehearing Statement.

Thus, one seeking to clone a gene would first seek to develop a DNA sequence for insertion into vectors. In 1983, there were three principal methods of doing so. When the entire amino acid sequence of the desired polypeptide product was known, the method of choice was frequently the chemical manufacture of a DNA sequence providing a code for that polypeptide. CX-1, col. 3, lines 17-20.

When the entire sequence was not known, one could attempt the _in vitro_ synthesis of a double-stranded DNA sequence by forming a DNA complement of messenger RNA that has been isolated from the donor cells (referred to as the "cDNA method"). CX-1, col. 3, lines 11-16, 43-48. Through the use of an enzyme known as reverse transcriptase, a cell's mRNA can be used to generate its complementary single-strand DNA sequence. Sadler, Tr. 812-813; Ullrich, Tr. 655-656; FF 158-160. A second enzyme then converts the single-stranded DNA into a double-stranded DNA molecule known as complementary DNA or cDNA. Sadler, Tr. 812-813; FF 160. In this manner, one makes what is referred to as a cDNA library. Davies, Tr. 475-476; FF 158-163. If the donor cell expresses only a small amount of a protein, the messenger RNA of interest will be in very low concentrations, and there is a possibility that the mRNA of interest will not be represented when the cDNA library is made. Davies, Tr. 476; FF 153-154, 164.

Where portions of the polypeptide's amino acid sequence are known, one would construct probes comprising sequences of nucleotides duplicating a sequence putatively present in the "target" cDNA. CX-1, col.3, lines 60-63; Sadler, Tr. 814; FF 168. The probes are labelled with a radioactive isotope. FF 183. The probes are utilized in screening procedures carried out on cDNA that has been denatured to single stranded form. Sadler, Tr.

817. During this procedure, a probe will hybridize, or bond, to its single stranded complement to produce a double-stranded DNA sequence. Id.; FF 183. For example, a probe of the nucleotide sequence TATATATA will hybridize to a single strand of DNA of the sequence ATATATAT. Sadler, Tr. 815. The radioactive label allows for subsequent detection of the double-stranded DNA sequence which is coded for the sequence of amino acids in the polypeptide. Ullrich, Tr. 688; Sadler, Tr. 814-820. This sequence may then be isolated, purified and cloned so that the host cell will express it. 17/

However, as noted above enriched sources of mRNA may not be readily available for constructing a cDNA library when the polypeptide of interest is not expressed in great amounts. Davies, Tr. 476. Another method for developing a specific DNA sequence for use in recombinant technology is the isolation of a double-stranded DNA sequence from the entire genome of the donor. Construction of a genomic DNA ("gDNA") library entails the removal of the total DNA from a given organism, dividing it into small pieces and placing them in individual phages (bacterial viruses), so one has a representation of the total genome of the organism in small fragments. Davies, Tr. 475.

Screening of a gDNA library is done with probes in the same manner as the screening of a cDNA library. Sadler, Tr. 814. However, a gDNA library is approximately 100 times larger and more complex than a cDNA library.

17/ Another method of detecting the mRNA of interest is through the use of antibodies produced by another animal when it is injected with the human protein. This will allow a researcher to isolate only the mRNA of interest. Davies, Tr. 476-479. However, purification of mRNA was not a practical alternative for attempting to isolate mammalian protein genes because RNA degrades very rapidly. Ullrich, Tr. 705; FF 167.

Lin, Tr. 285-286. Unlike a cDNA library, a gDNA library contains introns which are intervening sections of DNA occurring throughout a gene which do not code for an amino acid in the gene product. Wall, Tr. 612-614; FF 165. Because of the size and complexity of the sequence of a mammalian genomic DNA, it is more difficult to successfully isolate and hybridize a DNA sequence from a genomic library. Sadler, Tr. 812; CX-1, col. 4-5.

In the hybridization procedures for screening cDNA or gDNA libraries, one uses "mixed oligonucleotide probes." FF 168-170. These probes consist of short chains of nucleotides ("oligonucleotides"). Sadler, Tr. 804; FF 168-170. Each nucleotide is intended to hybridize with its complement in the codons -- T with A, C with G, etc. FF 168. The probes are constructed based on information concerning the supposed amino acid sequence of the protein for which the sought-after DNA sequence is encoded. Ullrich, Tr. 697-698. FF 172-173. Because a given sequence of amino acids may be present in more than one location of the DNA library, in the art of gene cloning it is desirable to utilize a probe which is as long as possible so as to increase the likelihood that the probe will hybridize only on the targeted gene. Ullrich, Tr. 698; FF 171. 18/ A shorter probe has reduced hybridization specificity, i.e. it may hybridize to portions of the DNA library in which you are not interested. Lin, Tr. 360.

Thus, to the extent one knows the amino acid sequence of a protein like EPO, it would be expected that one would know the sequence of nucleotides in the codons of the gene encoded for that protein. See Opn.

18/ In practice, at least two probes of different sequences are used. The presence of the cDNA or gDNA sequence of interest is confirmed when a particular site produces positive results for each probe. CX-1, col. 4, lines 39-48; Sadler, Tr. 894, 901; FF 177.

at 32-34. However, certain amino acids have more than one corresponding codon. Ullrich, Tr. 697. Therefore, to account for all possible nucleotide arrangements, a probe that is designed to hybridize to the codon corresponding to a particular amino acid may require several different versions, each comprising a different sequence of nucleotides. FF 173; See Opn. at 39. An amino acid sequence that requires several different versions of a probe is said to be highly degenerate. FF 171-172. Increasing the length of the probe tends to increase its degeneracy because each subsequent amino acid in the sequence may be encoded by more than one codon. Ullrich, Tr. 697. For example, a probe for the amino acid sequence comprising lysine (abbreviated "lys;" one possible codon), tryptophan ("trp;" one codon), alanine ("ala;" four codons) and tyrosine ("tyr;" two codons) [19/] would have a degeneracy of 8 (1x1x4x2=8). Extending the probe so it would include phenylalmine ("phe;" 2 codons) increases the probes degeneracy to 16 (1x1x4x2x2=16). See RX-97. A sequence that has 16 different nucleotide sequences is said to have 16-fold degeneracy and requires 16 different probes to account for all possible sequences. In practice, use of every sequence is technically unfeasible. Ullrich, Tr. 698. One often uses a "guess-mer" approach which does not encompass every possibility of the amino acid coding but is sufficiently long that it can absorb some errors. Sadler, Tr. 907. It is such a set of probes that is referred to as "mixed oligonucleotide probes." Sadler, Tr. 821-824. Procedures using mixed oligonucleotide probes have been used in detecting

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19/ A list of the abbreviations for all twenty amino acids is on page 3 of CPX-9, J.D. Watson, J. Tooze, and D.T. Kurtz, Recombinant DNA: A Short Course (1983).

cDNA clones derived from sources which provide extremely low amounts of mRNA sequences for the polypeptide of interest. Ullrich, Tr. 700; FF 170.

These cloning procedures require knowledge of either the entire sequence of nucleotides in the targeted DNA (method one) or the sequence of amino acids in the polypeptide of interest, e.g. erythropoietin (methods two and three). Prior to 1983, the sequence of amino acids in the gene encoded for EPO was unknown because the gene had yet to be isolated. CX-1. Successful cloning of the gene therefore required the use of oligonucleotide probes for screening a cDNA or gDNA library. Opn. at 37-41.

The construction of usable probes required knowledge of at least some of the amino acid sequence of EPO. <u>See</u> FF 171-172. In 1982-1983, the amino acid sequence of the EPO protein was known only to a very limited extent. Goldwasser, Tr. 52; Ullrich, Tr. 669. Attempts to clone the EPO gene with only the small amount of amino acid sequence then known met with failure. Davies, Tr. 480-482. However, increased knowledge of the amino acid sequence by no means guaranteed that one would have been able to successfully clone the gene. Davies, Tr. 501. As stated in the preface to the 1982 publication <u>Molecular Cloning: A Laboratory Manual</u> (RX-39):

> Although molecular cloning seems straightforward on paper, it is more difficult to put into practice. Most protocols involve a large number of individual steps and a problem with any one of them can lead the experimenter into difficulty.
>
> RX-39 at iii

Basically, the problem to be solved was to determine the amino acid sequence of the gene encoding for erythropoietin, to isolate the gene, to inject it into a vector molecule and transform or transfect a host cell so that the host cell would produce EPO in response to the gene's orders. One

seeking to solve this problem would look to the prior art in the areas of 1) methods of genetic engineering and 2) the amino acid structure of erythropoietin for constructing probes to screen DNA libraries. See Opn. at 35-41.

The filing of a patent application constitutes a constructive reduction to practice of the invention disclosed therein and may be relied upon to determine patentability. 3 Chisum Patents § 10.05 [1]; Hybritech v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 84, 87 (Fed. Cir. 1986).

The claims at issue of the '008 patent issued from U.S. Patent Application No. 675,298 filed on November 30, 1984. CX-1; FF 234. Application No. 675,298 is a continuation-in-part application of prior U.S. Patent Application No. 561,024 which was filed on December 13, 1983. CX-1, CX-2; FF 235. Pursuant to 35 U.S.C. § 120, the effective filing date of the '008 patent is December 13, 1983. While Dr. Lin apparently succeeded in isolating the gene for EPO in the latter portion of 1983 (Rathmann, Tr. 180; CX-192), the record is not clear as to exactly when Dr. Lin invented what is claimed in the '008 patent. Dr. Rathmann, president and chief executive officer of Amgen, testified that he was unable to remember the date of the first successful cloning of the EPO gene. Rathmann, Tr. 178. Therefore, the date of invention of the '008 patent is December 13, 1983 and the prior art will encompass patents, publications, etc. that were in existence prior to then.

Chugai has cited several pieces of prior art in support of its contention that the invention disclosed in the '008 patent would have been obvious to one of ordinary skill in the art when it was invented in the

fall of 1983. FF 414-423; 433-435. During the hearing, it called particular attention to the following:

RX-70 Suggs, et al. Use of synthetic oligonucleotides as hybridization probes: Isolation of cloned cDNA sequences for human beta2-microglobulin. (1981)

RX-71 Anderson, et al. Isolation of a genomic clone for bovine pancreatic trypsin inhibitor by using a unique-sequence synthetic DNA probe. (1983)

RX-74 Wallace, et al. Hybridization of synthetic oligodeoxyribonucleotides to phi chi 174 DNA: the effect of single base pair mismatch. (1979)

RX-75 Wallace, et al. The use of synthetic oligonucleotides as hybridization probes. II. Hybridization of oligonucleotides of mixed sequence to rabbit beta-globin DNA. (1981)

RX-78 Whitehead, et al. Use of a cDNA clone for the fourth component of human complement (C4) for analysis of a genetic deficiency of C4 in guinea pig. (1983)

RX-96 Jaye, et al. Isolation of a human anti-haemophilic factor IX cDNA clone using a unique 52-base synthetic oligonucleotide probe deduced from the amino acid sequence of bovine factor IX. (1983) Sadler, Tr. 828-834.

These items of prior art do not address the cloning of the gene encoding for erythropoietin. FF 423, 442. However, they generally describe the methodologies with respect to oligonucleotide probes for screening libraries prior to September, 1983. Sadler, Tr. 828. One of ordinary skill in the art seeking to clone a particular gene would look to references generally describing methods of gene cloning. References that are reasonably pertinent to the particular problem with which the inventor was involved are within the scope of the prior art for purposes of an obviousness analysis. Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.,

230 U.S.P.Q. 416 (Fed. Cir. 1986). Accordingly, it is proper to consider these references as within the scope of the prior art.

With regards to the amino acid sequence of EPO itself, none of the references cited by Chugai as prior art set forth this information. During 1982-1983, Amgen had available to it only limited sequence information from the region of the EPO protein known as the N-terminus. Goldwasser, Tr. 52. Dr. Lin testified that this sequence was only "about 20" amino acids long, Lin, Tr. 282. The prosecution history of the '008 patent establishes that the examiner was aware of a reference by Sue et al. that disclosed what were believed to be the first 26 amino acids in the EPO peptide. CX-2, 334. However, this information proved to be partially wrong. CX-2, 355-365; Davies, Tr. 480-481, 486-487. Scientists at Amgen constructed probes based upon this limited sequence information but were unable to isolate the EPO gene. Goldwasser, Tr. 52. Similarly, scientists at Biogen working with the Sue et al. reference were unable to clone the EPO gene. Davies, Tr. 481-487. FF 459-462. The prior art was nearly devoid of information regarding the amino acid sequence of erythropoietin.

2. Differences between the Prior Art and Claims at Issue

The claims at issue [20/] reflect the results of Amgen's genetic engineering efforts. Illustrative of the claims at issue are the following:

> 2. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin.
>
> 4. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to claim 1, 2

20/ At issue in this investigation are claims 2, 4-7, 23-25 and 27-29 of U.S. Letters Patent 4,703,008.

or 3 in a manner allowing the host cell to express erythropoietin.

5. A biologically functional circular plasmid or viral DNA vector including a DNA sequence according to claim 1, 2 or 3.

7. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin to allow possession of the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells and to increase hemoglobin synthesis or iron uptake.

23. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to claim 7, 8 or 11 in a manner allowing the host cell to express said polypeptide. CX-1

Figure 6 of the '008 patent identifies 166 specific amino acids in the primary amino acid sequence of mature human erythropoietin. CX-1.

Lin's general method for cloning the gene, viz. through the use of mixed oligonucleotide probes, was known in the art at the time. See RX-70, RX-71, etc. In support of its position that the '008 patent is invalid for obviousness, Chugai argues that the patent does not contribute anything to the art of gene cloning and the only difference between the claims at issue and the prior art is the particular sequence cloned and this difference is "insignificant." Chugai's Posthearing Brief, 27-30.

This argument is flawed in two respects. While references describing cloning procedures are reasonably pertinent to the problem facing Lin, it does not follow that utilization of these procedures by itself renders the purified and isolated amino acid sequence (or the vector including it and the transfected host cell) obvious. The patentability of a product does not depend on its method of production. It is the product itself which must be new and unobvious. See In re Thorpe, 227 U.S.P.Q. 964 (Fed. Cir.

1985); In re Pilkington, 162 U.S.P.Q. 145 (C.C.P.A. 1969). ("[P]atentability of a claim to a product does not rest merely on a difference in the method by which that product is made. Rather, it is the product itself which must be new and unobvious." 162 U.S.P.Q. at 147) Further, respondents' argument runs counter to the second sentence of § 103 which states that patentability shall not be negatived by the manner in which the invention was made. This sentence makes clear that patents are not granted only to those inventors who experience a "flash of genius." 1 Chisum, § 5.04[2]. One who invents a new and useful product will not be denied a patent simply because in the act of inventing it, he utilized scientific and technical principles known in the art.

The Federal Circuit has repeatedly held that an inventor's utilization of already known science and technology does not in itself establish that the invention would have been obvious. Lindemann Maschinenfabrik GmbH v. American Hoist and Derrick Co., 221 U.S.P.Q. 481 (Fed. Cir. 1984). In Panduit Corp. v. Dennison Manufacturing Co., 227 U.S.P.Q. 337, vacated 229 U.S.P.Q. 478, on remand 1 U.S.P.Q. 2d, 1593 (Fed. Cir. 1987), the Court found the district court's obviousness analysis erroneous because it emphasized what the trial court thought was taught by general engineering principles. In holding that such an approach was erroneous, the Federal Circuit stated:

> [I]t raises a standard impossible for any patent to meet. Humans do not create from nothing; they must employ the principles of engineering and physics and their experience. It cannot be the law that the only inventions patentable are those that cannot be explained by any known principles of engineering or physics.
>
> 227 U.S.P.Q. at 347

In _Loctite Corp. v. Ultraseal Ltd._, 228 U.S.P.Q. 90 (Fed. Cir. 1985), the Court of Appeals for the Federal Circuit vacated a trial court's finding of obviousness. The trial court had stated that the "'most critical evidence'" of obviousness was the inventor's testimony regarding the mental processes that led to the invention. 228 U.S.P.Q. at 99. The Federal Circuit stated that this evidence should not itself compel a conclusion of obviousness, citing the second sentence of § 103 as a reason. _Id._ In _Ex parte Petersen_, 228 U.S.P.Q. 216 (P.T.O. Bd. Pat. App. & Int. 1985), the patent examiner had rejected the inventor's claim under § 103 on the grounds that one of ordinary skill in the art could, via experimentation, produce the claimed invention. The Board of Patent Appeals and Interferences reversed this rejection, stating that the fact that the invention may have been the result of experimentation does not render it obvious, citing _In re Saether_, 181 U.S.P.Q. 36 (C.C.P.A. 1974). (argument that mere routine experimentation was involved in determining the optimized set of characteristics overlooks the second sentence of § 103). 228 U.S.P.Q. at 217.

Chugai's argument is further flawed because the test under § 103 is not whether an improvement or use set forth in a patent would have been obvious, but whether the claimed invention, considered _as a whole_ would have been obvious. 35 U.S.C. § 103. It is improper to consider the difference in a claimed invention from the prior art as the invention.

> "The 'difference' may have seemed slight (as has been the case with some of history's great inventions, e.g. the telephone), but it may have been the key to success and advancement in the art resulting from the invention. ... Hence the statute, the law established not by judges but by Congress, requires that the invention as claimed be considered "as a whole" when considering

> whether that invention would have been obvious when it was made. 35 U.S.C. § 103."

Jones v. Hardy, 220 U.S.P.Q. 1021, 1024 (Fed. Cir. 1984). See also Pacific Technica Corp. v. U.S., 3 U.S.P.Q. 2d 1168, 1180 (Ct. Cl. 1986).

Lin's invention, considered as a whole, is more than simply the application of certain known scientific principles and laboratory techniques to isolate a particular DNA sequence. Rather, Dr. Lin improved upon the known techniques by utilizing two probes of 128-fold degeneracy on a genomic library. FF 358, 361, 368, 369, 372-373, 391. With his improved technique, he was able to create a hitherto unknown isolated and purified strand of DNA and the host cell transformed or transfected with this DNA in a manner allowing the expression of erythropoietin. FF 105, 106, 109-111. Furthermore, the gene sequence isolated by Dr. Lin is more than just the results of his work but the groundwork for subsequent researchers desiring to clone the EPO gene. As noted by Dr. Ullrich, once a gene is isolated, the procedure used to find it in the first place is outdated. Ullrich, Tr. 674-675. There is no need for one seeking to clone the EPO gene to undertake the procedures Lin performed in determining the DNA sequence because the sequence is published in the patent. Ullrich, Tr. 675-676. It is this information about the structure of the gene encoded for EPO and the transformed or transfected cell that constitutes Lin's inventive contribution. Ullrich, Tr. 669; FF 449-451.

3. Level of Ordinary Skill in the Art

The parties are not in dispute regarding the very high level of ordinary skill in the art of recombinant DNA technology in 1982-1983. Typically, a person of ordinary skill in the art had a Ph.D. in the field

with one or two years of post-doctoral experience. Ullrich, Tr. 665; FF 449-451.

4. Objective Indicia of Obviousness

Under the test set forth in Graham v. John Deere, "secondary considerations" such as commercial success, long felt but unresolved needs, failure of others, etc. might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. 383 U.S. at 17-18. Since the enunciation of these considerations, the Federal Circuit has repeatedly held that these objective indicia of obviousness or nonobviousness must always be taken into account. See Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81 (Fed. Cir. 1986); Bausch & Lomb, Inc. v. Barnes-Hind, Inc., 230 U.S.P.Q. 416 (Fed. Cir. 1986). In order to be probative of nonobviousness, however, a sufficient nexus must be established between the objective indicia of nonobviousness and the merits of the claimed invention. Simmons Fastener Corp. v. Illinois Tool works, Inc., 222 U.S.P.Q. 744 (Fed. Cir. 1984).

5. Commercial success

The parties agree that erythropoietin produced by host cells transformed or transfected with the patented recombinant erythropoietin cannot be sold in the United States until approval is granted by the Food and Drug Administration ("FDA") and that the FDA has not granted approval to Amgen to market its product in the United States, although permission has been granted for the supply of small amounts for purposes of clinical trials. See Allegretti, Tr. 1482; Leonard, Tr. 1501-1502. Because there has been no commercial activity regarding recombinant erythropoietin, to

date there has been no commercial success (or lack thereof) with respect to this invention. Further, a hearing on the economic issues in this investigation was not conducted. See Opn. at 61-71. However, the description of the EPO market contained in the Business Week article that was Exhibit 5 to Amgen's complaint ("The Hormone That's Making Amgen Grow," Business Week, March 16, 1987) when read in light of the expert testimony regarding the long-felt need for recombinant EPO, leaves no doubt that the invention described in the '008 patent will enjoy considerable commercial success.

6. Long felt need

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.

Over a 20 year period (1961-1981), research was conducted involving sheep that showed when anemia was induced, the level of erythropoietin in their blood plasma 21/ increased. FF 95. Injecting this EPO-rich plasma into a different group of sheep with induced renal failure stimulated red blood cell production in the second group and alleviated their anemia. Eschbach, Tr. 545-546; FF 95. Similar work done on a limited scale with humans produced the same results. Eschbach, Tr. 547; FF 97. Thus, it became evident that injections of erythropoietin might be a possible therapy for anemia in humans with advanced renal disease or renal failure. Eschbach, Tr. 545-547.

In the past, severe anemia had been treated with blood transfusions or androgen (male hormone) therapy. Eschbach, Tr. 542; FF 83. In the early 1980's, there were three problems associated with transfusion therapy: the risk of infections (AIDS, hepatitis, etc.), sensitization to foreign proteins which can prevent a patient from later receiving a kidney transplant, and a buildup of iron in the system which can cause disorders of the heart, liver and/or pancreas. Eschbach, Tr. 557-558. Androgen therapy can result in unwanted facial hair, a "chipmunk-like" face, and liver changes. Eschbach, Tr. 558-559. "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

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21/ Plasma is the clear, yellowish fluid portion of blood in which the red cells are suspended. American Heritage Dictionary, 2d College ed. (1982), 948.

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).

7. Failure of others

With the advent of recombinant technology in the early 1980's, several biotechnology concerns devoted resources toward cloning the gene encoding for human erythropoietin. It was realized that the use of this new technology could result in the production of exogenous EPO in sufficient amounts to treat anemia. 22/ In addition to the work done by Amgen, efforts at cloning the EPO gene were made by Genentech, Inc. (Ullrich, Tr. 661-663), Genetics Institute, Inc. (Shoemaker, Tr. 880-909) and Biogen (Davies, Tr. 447).

The efforts of Biogen are illustrative of the commitment made by these concerns in their pursuit of the EPO gene. Commencing in 1981, Biogen

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22/ Because erythropoietin is a hormone, effective therapy requires continued injections so as to maintain the level of EPO in the patient's system. Discontinued therapy will result in a recurrence of the anemia. Eschbach, Tr. 560.

utilized the resources of three different laboratories: Biogen Laboratories in Geneva Switzerland under the direction of Dr. Julian Davies of the Institut Pasteur; the laboratory of Professor Bernard Mach at University of Geneva; and the laboratory of Professor Walter Gilbert, a Nobel laureate at Harvard University. Davies, Tr. 447-448; FF 455-456. Several other very highly qualified persons eventually became involved in the project. Davies, Tr. 448-449. Over the following three years, Biogen expended close to six million dollars in its unsuccessful efforts to clone the gene. Davies, Tr. 450; FF 452-471.

Similarly, a team of scientists at Genentech under the direction of Dr. Axel Ullrich spent two years on its project directed towards cloning the gene for EPO but were unable to succeed before Amgen. Ullrich, Tr. 661-663; FF 472-481. Another team of scientists under Dr. Ed Fritsch at Genetics Institute began an erythropoietin cloning project in 1982. Shoemaker, Tr. 888; FF 482-484. During the following one and one-half to two years Dr. Fritsch attempted to clone the gene through the use of mixed oligonucleotide probes but was also unsuccessful. Shoemaker, Tr. 888-889; FF 485. While Genetics Institute was eventually able to clone the gene, it did not do so before Amgen. Shoemaker, Tr. 896; FF 486.

The failure of others in the art to achieve the result achieved by the patentee is one of the objective indicia of nonobviousness set forth in Graham v. John Deere. In Panduit Corp. v. Dennison Mfg. Co., 227 U.S.P.Q. 337, the Federal Circuit noted that the patentee's competitors had invested several years and millions of dollars in unsuccessful efforts to achieve the invention disclosed in the patent. 226 U.S.P.Q. at 348-349. This "human, real world story in evidence" was "virtually irrefutable evidence"

that the invention of the patent in suit would not have been obvious to one of ordinary skill in the art at the time it was invented. Id.

The record in this investigation clearly shows that others in the art of recombinant technology, including scientists of the highest order, were unable to achieve the cloning of the EPO gene despite large expenditures of money, personnel and time.

8. Conclusion As To Obviousness

Dr. Lin's invention represents a significant contribution to the body of knowledge concerning recombinant genetics. The '008 patent teaches the structure of the gene encoding for human erythropoietin. Nowhere in the prior art is there a description of this gene's structure. FF 413. A limited amount of information on the amino acid sequence of EPO itself was available, but it proved to be incorrect and an inadequate tool for those seeking to clone the gene, and cannot be said to have taught one skilled in the art how to determine the gene's structure. Opn. at 44. The unobviousness of Dr. Lin's invention is strikingly apparent in light of the failure of other scientists, all of whom were of the highest caliber to succeed in isolating the gene encoded for erythropoietin. 23/ The failure of these scientists (who possessed more than the ordinary level of skill in the art) where Lin had succeeded demonstrates that Lin's invention would

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23/ Chugai argued that the cloning of the EPO gene by Dr. Ed Fritsch of Genetics Institute sometime after June of 1984 (CPX-34-3C at 14) is indicative of the obviousness of the Lin invention. However, near simultaneous and independent development is not necessarily indicative of obviousness, particularly in a rapidly developing field such as recombinant genetics. The Patent and Trademark Office has recognized this by providing for interference proceedings to determine the priority of invention between two pending applications. 35 U.S.C. § 135.

not have been obvious to one of ordinary skill at the time the invention was made.

B. The '008 Is Not Unenforceable For Inequitable Conduct.

Respondents charge that any claims in the '008 patent covering the process used to obtain positive clones of the EPO gene were obtained through inequitable conduct before the PTO during prosecution. Respondent's Pre-Hearing Statement, 66-72. If one charged with infringement is successful in raising the defense of inequitable conduct, the patent-in-suit is held unenforceable. 35 U.S.C. § 282; J.P. Stevens & Co., Inc. v. Lex Tex Ltd., Inc., 223 U.S.P.Q. 1089, 1093-94 (Fed. Cir. 1984). 24/

The Federal Circuit summarized the burden that must be carried in order to prove a charge of inequitable conduct as follows:

> To be guilty of inequitable conduct, one must have intended to act inequitably. Thus, one who alleges a "failure to disclose" form of inequitable conduct must offer clear and convincing proof of: (1) prior art or information that is material; (2) knowledge chargeable to the applicant of that prior art or information and of its materiality; and (3) failure of the applicant to disclose the art or information resulting from an intent to mislead the PTO.

FMC Corp. v. Manitowoc, Co. Inc., 5 U.S.P.Q.2d 1112, 1115 (Fed. Cir. 1987) (recently quoted in In re Harita, 6 U.S.P.Q.2d 1930, 1935 (Fed. Cir. 1988)). 25/ The charge may be rebutted by showing that the prior art or information was not material, that the applicant did not know of the

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24/ If there is inequitable conduct, the entire patent-in-suit is held unenforceable, even if the misconduct occurred only in connection with particular claims. J.P. Stevens, 223 U.S.P.Q. 1089, 1093-94 (Fed. Cir. 1984).

25/ The court stated that the "applicant" for purposes of the second element includes the patentee and the attorney who prosecuted the application of the patent-in-suit. 5 U.S.P.Q.2d at 1115 n.8.

material prior art or information or of its materiality, or that the failure to disclose was not the result of an intent to mislead the PTO. "Thus, a balancing of overlapping considerations is involved in determining, in view of all the circumstances, the presence or absence of inequitable conduct." FMC Corp., 5 U.S.P.Q.2d at 1115. The requirements of materiality and intent may be said to overlap because of inferences of intent that may be drawn from a high degree of materiality. FMC Corp., 5 U.S.P.Q.2d at 1116.

Inequitable conduct has not occurred unless there was intent to act inequitably. FMC Corp., 5 U.S.P.Q.2d at 1115. Simple negligence or an error in judgment is not sufficient for a holding of inequitable conduct. Akzo N.V. v. E.I. du Pont de Nemours, 1 U.S.P.Q.2d 1704, 1708 (Fed. Cir. 1987). Gross negligence exists when the applicant "judged as a reasonable person in his position, should have known the materiality of a withheld reference." J.P. Stevens, 223 U.S.P.Q. at 1092. Gross negligence must be defined "in terms of a particular act or acts viewed in light of all the circumstances." Kingsdown Medical Consultants, Ltd. v. Hollister Inc., No. 88-1265, slip op. at 19 (Fed Cir. Dec. 21, 1988) (section en banc). Gross negligence "does not of itself justify an inference of intent to deceive; the involved conduct, viewed in light of all the evidence, including evidence indicative of good faith, must indicate sufficient culpability to require a finding of intent to deceive." Id. 26/ The ultimate question of

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26/ Even an applicant (or one whose actions are chargeable to the applicant) who knew or should have known of the materiality of an undisclosed piece of prior art or information is not precluded from attempting to show that he did not intend to mislead the PTO. Although, a high level of materiality may make it difficult to demonstrate "subjective good faith" adequately to prevent an inference of intent to mislead. FMC Corp., 5 U.S.P.Q.2d at 1116. See Burlington Industries Inc. v. Dayco

whether inequitable conduct occurred is equitable in nature, rather than a question of law. Id.

At issue in this investigation is whether the applicant failed to disclose to the examiner during prosecution of the '008 patent how the human gDNA and the monkey cDNA libraries were screened for EPO gene clones, and whether any false or withheld information would have been material to the issuance of the '008 patent.

Two pools of 128 mixed oligonucleotide probes were used to screen the human gDNA library. FF 370, 372. This initial screening of the 1.5 million phage library yielded about 40 putative clones. FF 381-386. Then, subscreening was performed with a set of 48 mixed probes at a lower plating density. FF 389. The subscreening is routine in the screening process, and known to one skilled in the art. Lin, Tr. 372. Through subscreening, three positive clones were obtained. FF 388. It is complainant's position that although subscreening was used, the initial screening identified the positive clones and made it possible to isolate them. (RX 11C - C.H. Lin Dep. at 138-144; Lin Tr. 364-375; Shoemaker Tr. 920-921; CX1 col. 13, lines 43-51, col. 39, lines 49-60.)

The 200,000 colony monkey kidney cDNA library was screened with a single pool of 128 mixed oligonucleotide probes. A subset of 16 mixed oligonucleotide probes was then used to arrive at the positive clones. The subset of 16 probe sequences was obtained by the use of the northern blot method. One of the 8 subpools of 16 probe sequences hybridized to messenger RNA in the phenylhydrazine induced monkey kidney but not in the

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Corp., 849 F.2d 1418, 7 U.S.P.Q.2d 1158, 1160 (Fed. Cir. 1988); J.P. Stevens, 223 U.S.P.Q. at 1096-98.

normal monkey kidney. This technique allowed the selection of the 16 probe sequence most likely to identify a positive clone. Seven positive clones were obtained. (Lin Tr. 354; Shoemaker Tr. 917-919; Ullrich Tr. 720-728; CX2, pp. 356-57.)

In neither the specification that issued, nor in the prosecution history, is it stated that subscreening (or rescreening) procedures were used to obtain the positive human clones, or that the 128 probes used to screen the monkey cDNA library were narrowed down to 16 by the use of a method already known to one skilled in the art. (See CX1 col. 18, lines 1 -64; col. 20, line 50 - col. 21, line 16; CX2, pp. 356-57, 364, 440-41.) The applicant's omissions occurred after a rejection of claims that may have covered the probing processes used to isolate the positive clones. (See CX2, pp. 355-56.)

The issue presented by these facts is whether the withheld information concerning additional screening steps would have been material to the issuance of the '008 patent, and if so, whether the applicant acted with the requisite intent, as described above.

The "major standard" used by the Federal Circuit for materiality "is whether a reasonable examiner would consider the omission or misrepresentation important in deciding whether to issue the patent." This standard is identical to the PTO standard of materiality (37 C.F.R. §1.56). Akzo N.V. v. USITC, 1 U.S.P.Q.2d 1241, 1247 & n.14 (Fed. Cir. 1986), cert. denied, 107 S.Ct. 2490, 96 L.Ed.2d 382 (1987); American Hoist & Derrick Co. v. Sowa & Sons, Inc., 220 U.S.P.Q. 763, 773 (Fed. Cir.), cert. denied, 469 U.S. 821 (1984).

In this instance, the applicant cancelled (without prejudice) the rejected claims with respect to which he had allegedly committed inequitable conduct. The applicant also added new claims. (CX2, p. 434.) The claims that did issue in the '008 patent do not cover the process by which positive clones for the EPO gene were obtained. 27/

It cannot be said that a reasonable examiner would have considered the details of the processes used to obtain positive clones important in deciding whether to issue the '008 patent. It has not been shown that information regarding the subscreening would have been material to the prosecution of the '008 product claims. "[M]ateriality is a necessary ingredient of any inequitable conduct." J.P. Stevens, 223 U.S.P.Q. at 1093 n.7. Since there are no process claims in the '008 patent, there is no clear and convincing evidence of inequitable conduct to obtain the issuance of the '008 patent. The '008 patent is therefore enforceable.

IV. INFRINGEMENT

The parties have stipulated that Chugai manufactures recombinant erythropoietin in Japan through the use of host cells. CX-85. Further, Chugai has admitted that it utilizes host cells in the manufacture of recombinant EPO that have been transformed or transfected with a vector containing a DNA sequence encoding for EPO. CX-181.

In February, 1986, Chugai completed the construction of a production facility for the manufacture of human erythropoietin in Ukima, Japan. FF 509-510. Since at least April, 1986, the facility in Ukima has been used for the manufacture of human EPO. FF 511. Genetics Institute has

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27/ See the discussion of claim construction, pp. 21-25. See CX2, p. 356.

been the sole source of the host cells used by Chugai in its production of EPO. FF 512.

The details of Chugai's production process (FF 515-568) were studied by Amgen's expert, Dr. T. Randolph Wall. FF 569. Dr. Wall testified that Chugai utilized a purified and isolated DNA sequence encoding a polypeptide with the biological activities of EPO as claimed by Claim 7 of the '008 patent. FF 572-573. The Chugai host cells have been transformed or transfected with a DNA sequence encoding for EPO in a manner allowing them to express EPO and are therefore described by claim 23 of the '008 patent. Wall, Tr. 606-607; FF 574. Aspects of Chugai's host cells are described in claims 28 (biologically active vector including the sequence described in claim 7) and 29 (eucaryotic, e.g. mammalian, host cell which is stably transformed or transfected with a DNA vector as described in claims 28 and 7) of the '008 patent. FF 576-579. In light of the parties' stipulation and the testimony of Dr. Wall, there is no question that Chugai utilizes the invention of Amgen's that is described in the '008 patent.

The use of a patented product like that described in the claims of the '008 patent constitutes patent infringement if done in the United States. 35 U.S.C. § 271. Use of the claimed host cell in the United States to make EPO would be an infringement of the '008 patent. Rzucidlo, Tr. 1175. However, use of a patented product abroad does not violate 35 U.S.C. § 271. See Deepsouth Packing v. Laitram Corp., 406 U.S. 518 (1972) (overseas assembly and use of patented machines do not constitute an infringement).

This investigation is directed towards imported recombinant erythropoietin, a product which is not claimed by the '008 patent. The claims of the '008 patent do not cover a process which is used to

manufacture EPO. 28/ Rather they cover articles, including purified and isolated DNA sequences, vectors including said sequences host cells transformed or transfected with said sequences in a manner allowing the host cells to express EPO. CX-1; Opn. at 21-25. Accordingly, there is no infringement of the '008 patent.

V. DOMESTIC INDUSTRY

A. Requirement Of A Domestic Industry Under The Trade Act

On August 23, 1988, the President signed into law the Omnibus Trade and Competitiveness Act of 1988 ("Trade Act"). The Trade Act amended 19 U.S.C. § 1337 in relevant part as follows:

> (a)(1) Subject to paragraph (2), the following are unlawful, and when found by the Commission to exist shall be dealt with, in addition to any other provision of law, as provided in this section:
>
> (A) Unfair methods of competition and unfair acts in the importation of articles (other than articles provided for in subparagraphs (B), (C), and (D)) into the United States, or in the sale of such articles by the owner, importer, or consignee, the threat or effect of which is --
>
> (i) to destroy or substantially injure an industry in the United States;
>
> (ii) to prevent the establishment of such an industry; or
>
> (iii) to restrain or monopolize trade and commerce in the United States.
>
> (B) The importation into the United States, the sale for importation, or the sale within the United States after importation by the owner, importer, or consignee, of articles that --

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28/ Importation of a product made by a patented process would constitute infringement. 35 U.S.C. 271(g).

(i) infringe a valid and enforceable United States patent or a valid and enforceable United States copyright registered under title 17, United States Code; or

(ii) are made, produced, processed, or mined under, or by means of, a process covered by the claims of a valid and enforceable United States patent. ...

(2) Subparagraphs (B), (C), and (D) 29/, of paragraph (1) apply only if an industry in the United States, relating to the articles protected by the patent, copyright, trademark, or mask work concerned, exists or is in the process of being established.

(3) For purposes of paragraph (2), an industry in the United States shall be considered to exist if there is in the United States, with respect to the articles protected by the patent, copyright, trademark, or mask work concerned --

(A) significant investment in plant and equipment;

(B) significant employment of labor or capital; or

(C) substantial investment in its exploitation, including engineering, research and development, or licensing.

Trade Act, § 1342

The amendments to § 337 effected by the Trade Act also eliminated the requirement that a complainant prove that the domestic industry is economically and efficiently operated.

B. Amgen's Motion For Summary Determination

On August 15, 1988, Complainant Amgen, Inc. ("Amgen") moved to terminate this investigation with respect to the economic issues. Motion

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29/ Subparagraphs (C) and (D) declare unlawful the importation into the United States, the sale for importation, or the sale within the United States of articles that infringe valid and enforceable registered trademarks and mask works.

Docket No. 281-55. On September 28, 1988 the Administrative Law Judge held oral argument on Motion 281-55.

Amgen asserted that it satisfies the criterion set forth in § 1337(a)(3)(A) which states that a domestic industry shall be found to exist when there has been a significant investment in plant and equipment with respect to the articles protected by the patent concerned. 30/ In support of this assertion, Amgen referred to its plant in Thousand Oaks, California. This plant is 24,000 square feet in size and was constructed at a cost of approximately $20 million. May affidavit; Complaint Exhibits 11 and 12.

In its opposition to Amgen's motion, Chugai asserted that a hearing was necessary because an accurate measurement of Amgen's investment required a determination of that portion of Amgen's plant in which the patented host cells were actually used and the amount and nature of Amgen's investment therein. Respondents' Response in Opposition to Motion 281-55 at 9 - 10. Chugai's argument is premised on an interpretation of § 1337 (a)(3)(A) that would allow only that portion of a complainant's plant where the patented invention was located to be considered when determining whether a domestic industry exists.

When Congress amended § 337 through the Trade act, it expressed its concern that the Commission had, on occasion, defined "domestic industry"

30/Because subparagraphs (A), (B) and (C) of paragraph (3) are set forth in the disjunctive, a complainant in a patent-based § 337 investigation needs to satisfy the criteria of only one of the subparagraphs in order to establish the existence of an industry for purposes of § 337.

too narrowly. H.R. Rep. No. 40, 100th Cong., 1st Sess. 157 (1987)[31]/ Therefore, in § 1337(a)(3), Congress enumerated specific activities which, when undertaken "with respect" to the articles protected by the patent, would mandate the finding of a domestic industry. The inclusion of significant investment in plant and equipment (19 U.S.C. § 1337 (a)(3)(A)) in the determination of "domestic industry" reflects existing Commission practice. Id., 157. See, Certain Dynamic Random Access Memories, Components Thereof, and Products Containing Same ("DRAMS"), ITC Inv. No. 337-TA-242, Commission Opinion at 62.

The Supreme Court has repeatedly stated that a statute is to be interpreted in light of the purpose Congress sought to serve. Chapman v. Houston Welfare Rights Organization, 441 U.S. 600 (1979). Moreover, it is the duty of a court interpreting a statute to do so in the manner most harmonious with its scheme and with the general purposes Congress manifested. Commissioner of Internal Revenue v. Engle, 464 U.S. 206 (1984). The circumstances of the enactment of a particular statute may be particularly relevant to this inquiry. Watt v. Alaska, 451 U.S. 259 (1981).

In the Trade Act, Congress stated that it found the existing protection under § 337 inadequate. Its stated purpose for amending the law was to make it a more effective remedy for the protection of United States intellectual property rights. H.R. 4848, 100th Cong., 2d Sess. § 1341. To this end, Congress enumerated certain circumstances which, when found to

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31/The legislative history of the Trade Act includes the legislative history of H.R. 3, Trade and International Economic Policy Reform Act of 1987. See Trade Act, § 2. This report of the Committee on Ways and Means of the U.S. House of Representatives accompanying H.R. 3 and is therefore part of the Trade Act's legislative history.

exist with respect to the articles protected by the patent, would require a finding that a domestic industry exists. 19 U.S.C. § 1337(a)(3).

The Commission has often stated that when determining whether a domestic industry exists, its practice is not to adhere to any rigid formula but to examine each case in light of the realities of the marketplace. See DRAMS at 61. In patent-based investigations, the Commission has in the past defined the domestic industry as the domestic operations of the complainant and its licensees devoted to the exploitation of the patent at issue. The scope of the domestic industry encompassed not only manufacturing, but could also include distribution, research and development and sales. Id. at 62; see also, Schaper Manufacturing Co. v. U.S. International Trade Commission, 219 U.S.P.Q. 665, 668-669 (Fed. Cir. 1983) (non-manufacturing activities may constitute part of domestic industry).

It has been Commission practice to find that a domestic industry exists when there has been a significant investment in plant and equipment devoted to the exploitation of the patent at issue. See, In the Matter of Certain Plastic Fasteners, Inv. No. 337-TA-248. The inquiry into whether a domestic industry exists is not restricted to a narrowly-focused view of the amount of resources expended in the actual use of the patent. Instead, the Commission inquires into the exploitation of the patent. For example, in Plastic Fasteners, the complainant owned a patent on a process of manufacturing plastic items for attaching items such as garment tags. The domestic industry that was found to exist comprised more, than just the portion of the plant where the patented process was utilized and those employees who directly utilized it. Instead, the entire plant and its

employees, as well as employees and facilities located in other cities engaged in warehousing, were considered part of the domestic industry. This approach is in accordance with the Commission practice of looking at the exploitation of the patented invention as a whole, not just a tightly circumscribed view of its use.

It has not been disputed that Amgen's plant (known as "Building No. 6") is devoted to the manufacture of recombinant human erythropoietin. The Establishment Licensing Application ("ELA") submitted by Amgen to the Food and Drug Administration ("FDA") states that the facility is "dedicated solely to the production of [recombinant human erythropoietin]." Exhibit H to Staff Response to Motion 281-55. In order to manufacture a product other than recombinant human EPO in Building No. 6, Amgen would be required to file an amendment to its ELA with the FDA. Weist Deposition at 212; Johnson Deposition at 76; (Exhibit I to Staff's Response to Motion 281-55. Because Amgen has not filed any such amendment with the FDA regarding Building No. 6, Id., there is no question that the entire facility is currently devoted to the manufacture of EPO. In light of the evident intent of Congress in amending § 337 and earlier Commission decisions regarding the definition of "domestic industry," all of Amgen's investment in Building No. 6 is to be considered.

Chugai further argued that it was impossible to determine the amount that Amgen has truly invested in Building No. 6, and therefore a hearing into this issue was required. The equipment in the building has been sold for approximately $11.3 million to Maryland National Leasing Co. ("Maryland National") which has leased it back to Amgen. Weist Deposition, 59 (Exhibit A to Chugai's Response to Motion 281-55), Hays Affidavit (Exhibit

D to Chugai's Response to Motion 281-55). Chugai argues that because title to the equipment has passed to Maryland National, it is Maryland National, not Amgen, which has invested in the Building No. 6 equipment.

The standard accounting principles as set forth by the Financial Accounting Standards Board state that a lease is to be treated as a capital lease if it meets any one of the following four classification criteria:

1. The lease transfers ownership of the property to the lessee by the end of the lease term.

2. The lease contains an option to purchase the leased property at a bargain price.

3. The lease term is equal to or greater than 75 percent of the estimated economic life of the leased property.

4. The present value of rental and other minimum lease payments equals or exceeds 90 percent of the fair value of the leased property less any investment tax credit retained by the lessor.

Financial Accounting Standards Board ("FASB"), Accounting Standards - General Standards, 29141 (1986-87 ed.)

The term of Amgen's lease with Maryland National is approximately seven years. May Deposition, 62. At the end of the lease's term, Amgen may purchase the equipment from Maryland National at a nominal price. Id. The economic life of the equipment that is the subject of the lease is approximately eight to nine years. Id.

Because the leasing agreement between Amgen and Maryland National provides for a nominal purchase of the equipment at the end of the lease and the lease's term (7 years) is at least 75% of the equipment's economic life (9 years), the lease satisfies the second and third classification criteria of the FASB. Therefore, it is proper to classify this agreement as a capital lease. Such a lease transfers substantially all the risks and benefits of ownership to Amgen and is therefore properly accounted for as

the acquisition of an asset and the incurrence of an obligation. FASB Standards, 29141. This conclusion is supported by Amgen's outside accounting firm which rendered an opinion that the Amgen/Maryland National agreement is in fact a loan. May Deposition, 61-62. Accordingly, it is appropriate to consider the $11.3 million dollars in equipment which is the subject of the agreement as part of Amgen's investment in plant and equipment for purposes of determining whether a domestic industry exists.

Chugai further asserted in its response to Motion 281-55 that because Amgen has recouped part of its initial investment in Building No. 6, that amount should not be considered when computing the amount of complainant's investment for purposes of determining whether a domestic industry exists. Chugai asserted that because Amgen has recouped a portion of its initial investment in the plant through the sale of the plant's design and specifications to the Ortho Pharmaceutical Co. ("Ortho"), these recouped monies should be deducted from the initial investment with the remainder constituting Amgen's "investment" for purposes of determining the existence of a domestic industry.

This argument is unpersuasive. Even if Amgen has recouped a portion of the cost of its initial investment, it does not follow that the investment has undergone a corresponding decrease in value or that the size of the domestic industry has been diminished. Application of Chugai's argument would require a finding of no domestic industry in every instance where the complainant has recouped his initial investment. It would be contrary to the intent of § 337 to find that no domestic industry exists and thus deny relief because the complainant has achieved the legitimate business goal of recouping or reducing its initial investment.

Amgen's investment in plant and equipment is considered a capital investment, and there is no reason to deduct any amount from the $20 million expended by Amgen because of its sale and leaseback agreement with Maryland National (Opn.at 66-68) or because it has recouped some of its initial investment. Opn. at 68. Accordingly, for purposes of determining the existence of a domestic industry the entire $20 million initial investment in plant and equipment will be considered.

While Congress, in amending § 337, did not set forth specific monetary levels that would constitute a "significant" investment, Amgen's $20 million investment in plant and equipment is greater than the investment made by other complainants in pre-Act investigations. See, Certain Softballs and Polyurethane Cores Therefor, Inv. No. 337-TA-190. While the domestic industry determinations in these investigations were made after examining more than just the complainant's investment in plant and equipment, they serve as guidelines for domestic industry determinations under the new law. In light of these earlier determinations and the express will of Congress to expand the definition of "domestic industry," Amgen's $20 million investment constitutes a "significant" investment in plant and equipment for purposes of § 1337 (a)(3)(A).

C. Law of Summary Determination

Commission Rule 210.50(a) (19 C.F.R. § 210.51(a)) states that any party may move for summary determination in his favor upon all or any part of the issues to be determined in the investigation. The motion must be filed no less than thirty days before the date fixed for hearing. The Commission's rule is patterned after Rule 56 of the Federal Rules of Civil Procedure and, like Rule 56, is designed to dispose of actions without a

hearing when there is no genuine issue of material fact. "The determination sought by the moving party shall be rendered if the pleadings and any depositions, admissions on file, and affidavits show that there is no genuine issue as to any material fact and that the moving party is entitled to a summary determination as a matter of law." 19 C.F.R. § 210.50(b).

The administrative law judge, in ruling on a motion for summary determination, is to determine whether such a genuine issue exists, not to resolve any existing factual issues. 6 Moore's Federal Practice para. 56.15[1][1.-0] and cases cited therein. The moving party has the burden of clearly establishing the absence of any genuine issue, and all factual inferences must be viewed in a light most favorable to the party opposing the motion. Id. paras. 56.15[3], 56.15[8]. However, the adverse party cannot rest upon the allegations in its pleadings, but must present sufficient evidence to raise a triable issue of material fact. Id. para. 56.15[3].

Any reasonable doubt as to the existence of a triable issue of material fact should be resolved against the movant. That does not mean that the Administrative Law Judge should be unduly reluctant to grant summary determination when a hearing would serve no useful purpose and the movant is entitled to judgment as a matter of law. See id. par. 56.02[1]. A summary determination results from an application of substantive law to facts that are established beyond reasonable controversy.

D. Conclusion

Amgen has demonstrated beyond reasonable controversy that its Building No. 6 constitutes a significant investment in plant and equipment with

respect to the patent at issue in this investigation. When the existence of a significant investment in plant and equipment with respect to the articles protected by the patent has been established, § 1337(a)(3)(A) mandates the determination that a domestic industry exists. In applying the statute to the facts concerning Amgen's investment in Building No. 6, summary determination that there is a domestic industry with respect to the articles protected by the '008 patent is appropriate. Accordingly, the Administrative Law Judge orally granted Amgen's motion for summary determination on the issue of the existence of a domestic industry immediately following the argument on September 23, 1988, and reaffirms that ruling herein.

FINDINGS OF FACT

I. BACKGROUND OF THE INVESTIGATION

1. This investigation was instituted upon the complaint of Amgen, Inc. ("Amgen") seeking relief under section 337 of the Tariff Act of 1930, as amended (19 U.S.C. §§ 1337 and 1337a). The alleged "unfair act" of respondents Chugai Pharmaceutical Co., Ltd. and Chugai U.S.A., Inc. (sometimes collectively referred to herein as "respondents" or "Chugai") is the importation of recombinant EPO, manufactured in Japan by Chugai using recombinant technology. 53 Fed. Reg. 3947 (February 10, 1988).

2. On August 23, 1988, the Omnibus Trade and Competitiveness Act of 1988 ("Trade Act") was enacted into law, amending § 337. In light of the amendments, the Notice of Investigation was amended to state that this investigation was being conducted under 19 U.S.C. § 1337 (a)(1)(B)(ii), the statutory provision incorporating former § 1337a. 53 Fed. Reg. 47588 (November 23, 1988).

3. Amgen asserts that Chugai manufactures its product by a process covered by claims 2, 4-7, 23-25 and 27-29 of its Lin U.S. Patent 4,703,008 ("'008 patent"). 53 Fed. Reg. 3947 (February 10, 1988)

II. THE PARTIES

A. Amgen

4. Amgen Inc. ("Amgen") is a domestic corporation organized under the laws of the State of Delaware whose principal place of business is Thousand Oaks, California. Since its inception, Amgen has been involved in the research and development of pharmaceutical products based on recombinant DNA technology (also known as biotechnology). The first of

these products which Amgen expects to market in the United States is recombinant human erythropoietin, a hormone or glycoprotein which controls human red blood cell production. (CX-104)

5. Amgen was founded October 1, 1980, by a group including Dr. George Rathmann who is the chairman, president and chief executive officer of Amgen. (Rathmann, Tr. 168-170)

6. Dr. Rathmann has a Ph.D. in physical chemistry from Princeton University. His experience in research began in 1951 with 3M Company. After working at 3M for 20 years, he then worked at Litton Industries and became president of Litton Medical Systems. His other experience before Amgen includes Vice-President, Research and Development, Diagnostics Division, Abbott Laboratories. All of his positions involved interaction with or supervision of high technology research. (Rathmann, Tr. 168; CX-104C)

7. At the time of its founding, Amgen expected to make contributions not only in the pharmaceutical field, but also in other fields based on recombinant technology. (Rathmann, Tr. 171)

8. At its inception and for the purpose of accomplishing its goals, Amgen hired Ph.D. molecular biologists along with scientists from related disciplines. (Rathmann, Tr. 172)

9. During 1980, recombinant erythropoietin was first identified as a product goal for Amgen. This goal was identified in Amgen's original offering that was used to raise funding for Amgen in February of 1981. (Rathmann, Tr. 173)

10. Among the persons ..) Amgen first hired was Dr. Fu-Kuen Lin whose assignment, after being hirec ,n 1981, was to solve the problem of

determining a way to make recombinant human erythropoietin. (Rathmann, Tr. 173; Lin, Tr. 379)

11. In 1984, in order to obtain financing for its activities with respect to recombinant EPO, Amgen elected to form a joint venture with Kirin of Japan. The joint venture is a California corporation named Kirin-Amgen, Inc. George B. Rathmann was named President and CEO of the joint venture corporation. To the extent lawful patent rights existed Amgen and Kirin would control the erythropoietin markets. Pursuant to the agreement with Kirin-Amgen, Amgen, Inc. maintained control of recombinant EPO in the United States, the Japanese market for erythropoietin would be controlled by Kirin, and Amgen and Kirin would divide up the rest of the world. (Rathmann, Tr. 184-185).

12. A patent was procured in Dr. Lin's name, U.S. Patent No. 4,703,008 ("'008 patent"), entitled "DNA Sequences Encoding Erythropoietin." The '008 patent was issued on October 27, 1987. (Rathmann, Tr. 182; CX-1)

13. Dr. Lin assigned the '008 patent to Kirin-Amgen. Kirin-Amgen later assigned the patent to Amgen. (CX-1; Rathmann, Tr. 184-185).

14. Amgen has transferred cells used to express erythropoietin in a commercial operation to Kirin in Japan. (Rathmann, Tr. 218).

B. <u>Chugai/Chugai U.S.A.</u>

15. Chugai Pharmaceutical Co., Ltd. is a Japanese manufacturer of pharmaceutical products. Chugai U.S.A., Inc. is a U.S.-based subsidiary of Chugai Pharmaceutical Co., Ltd. and is owned entirely by Chugai Pharmaceutical Co., Ltd. (CX-171; CPX-6 (Morita Dep.), at 138) (Chugai

Pharmaceutical Co., Ltd. and Chugai U.S.A. Inc. are hereinafter referred to collectively as "Chugai".)

16. Genetics Institute ("G.I.") is a U.S. corporation based in Massachusetts which has entered into agreements with Chugai Pharmaceutical Co. Ltd. Under the agreements, G.I. collaborated with Chugai and transferred certain technology concerning recombinant erythropoietin and the process for manufacture of recombinant erythropoietin to Chugai. (CX-10C; CX-11C)

III. RESPONDENTS' ACTIVITIES

17. Chugai Pharmaceutical Co., Ltd. and Chugai U.S.A., Inc. import recombinant erythropoietin, which is the subject matter of this Investigation, into the United States. (CX-85; CPX-76 (Kawaguchi Dep.) at 231)

18. Chugai Pharmaceutical Co., Ltd. ("Chugai") obtained its recombinant EPO technology from Genetics Institute ("GI") which it used to produce EPO in Japan. (Shoemaker, Tr. 915).

19. Chugai did not obtain its technology from Amgen, i.e., Amgen did not transfer technology to Chugai, nor did Chugai "go into Amgen's plants and steal Amgen's technology." (Rathmann, Tr. 210).

A. Chugai - Genetics Institute Collaboration

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Additionally, G.I. published an article describing the DNA sequence for erythropoietin in the February 28, 1985 issue of Nature. G.I. tried to publish the article related to its cloning of EPO as soon as it was practical. (CX-13C; CX-20; CPX-1; Shoemaker, Tr. 973)

30. In the same issue of Nature in which G.I. published its article describing the DNA sequence for erythropoietin that it had isolated, Amgen announced the availability for the first time of recombinant EPO for research purposes. (Rathmann, Tr. 210-211 and 217; CPX-1; CX-20)

31. In Dr. Shoemaker's opinion, G.I. would not have terminated its EPO project, even if it had learned that Amgen had successfully cloned the EPO gene first. Dr. Shoemaker was one of the G.I. researchers who worked on the EPO project at G.I. (Shoemaker, Tr. 971-973; CX-12C at 2)

32. On January 3, 1985, G.I. filed its first patent application containing claims directed to a host cell for the production of recombinant erythropoietin. (Shoemaker, Tr. 974; CX-82)

33. G.I.'s filing date was more than one year after Amgen filed its first patent application directed to the production of recombinant EPO on December 13, 1983. (CX-1; CX-2)

34. The G.I. patent application for Cloned Human Erythropoietin and Products Thereof was filed in the name of Edward Fritsch, Robert P. Hewick and Kenneth Jacobs on January 3, 1985 as U.S. Ser. No. 688,622 which is

also known as international application PCT/US 8502405. (CX-82 at 1, CPX-34-3C (Fritsch Dep.), at 154 and Ex. 602)

35. The G.I. patent application for EPO included claims to a Chinese Hamster Ovary (CHO) host cell transformed or transfected with the EPO gene. (CX-82 at pp. 49-50)

36. The G.I. patent application for EPO states, in the Field Of The Invention, as follows:

> The present invention is directed to cloned genes for human erythropoietin that provide surprisingly high expression levels, to the expression of said genes and to the *in vitro* production of active human erythropoietin.

(CX-82 at 1)

37. The Summary Of The Invention in the G.I. patent application states as follows:

> The present invention is directed to the cloning of a gene that expresses surprisingly high levels of human EPO, the expression thereof, and the mass production *in vitro* of active human EPO therefrom.

(CX-82 at 4)

38. Examples 10 through 14 of the G.I. patent application described in detail various examples of expression of EPO by host cells which have been transformed or transfected with the DNA sequence for EPO. The result of the expression was production of recombinant EPO. (CX-82 at 32-42)

39. Dr. Fritsch stated that the scientific advances set forth in the G.I. patent application include:

(a) understanding the isolation of the erythropoietin gene,

(b) the understanding of the organization of the gene structure of EPO,

(c) the identification of both cDNA and genomic DNA demonstrated to produce EPO upon transfer to a mammalian cell system,

(d) the complete amino acid sequence of EPO, and

(e) demonstration of the feasibility of using distinct but degenerate oligonucleotide probes to isolate a gene.

(CPX-34-3C (Fritsch Dep.), at 156 and 162)

40. Dr. Fritsch, upon review of the Lin '008 patent, stated that it too disclosed scientific advances which are similar to those disclosed in the G.I. patent application including:

(a) the identification of the genomic clone containing sequences coding for EPO,

(b) the demonstration of the use of distinct oligonucleotide probes to isolate an EPO genomic DNA,

(c) the deduction of an amino acid sequence for EPO based upon the genomic DNA sequence.

(CPX-34-3C (Fritsch Dep.), at 169-170)

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44. In Chugai's 1985 Annual Report, it indicated that it was going to increase its overseas presence and, specifically, open an office in the United States under the name Chugai U.S.A. in April of 1986. (CX-171 at 4)

45. Chugai recognized that biotechnology was going to be the technology for creating new material in the pharmaceutical industry in the near future and Chugai intended to be "in the lime light" in the field of EPO. (CX-184CT)

> "It cannot be doubted and it also cannot be avoided that biotechnology will become the technology for creating new material in the pharmaceutical industry in the near future. In addition, in reality, it seems to mean that having this technology will enable enterprises to become larger. With this in view, it will be a good time to look at this technology carefully."

(CX-184CT at 3151)

> "Of course, biotechnology is not a cure-all method for pharmaceutical production, however, it is a very useful technology as a mass production method, and when a minute quantity of a living body component is needed for study is difficult to obtain."

(CX-184CT at 3158)

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62. In 1984, about 9 months after Amgen cloned the EPO gene, G.I., a company in the United States, isolated the DNA sequences encoding for EPO, incorporated the purified and isolated sequences into plasmids, and transfected host cells with those plasmids. The host cell line for producing EPO was subsequently transferred to Chugai prior to the issuance of the '008 patent. (Wall, Tr. 631; finding 444, infra).

63. Chugai has never transfected or transformed a procaryotic or eucaryotic host cell with a DNA sequence encoding EPO, which was used in manufacturing EPO. (RX-24 - Request for Admission No. 8).

64. Chugai has never made a biologically functional circular plasmid

or viral DNA vector including a DNA sequence encoding EPO, which was used in manufacturing recombinant EPO. (RX-24 - Request for Admission No. 9).

65. The DNA sequence in the host cells used by Chugai to make EPO in japan is a human cDNA sequence. (RX-24 - Request for Admission No. 16).

66. The recombinant erythropoietin imported into the United States by Chugai Pharmaceutical Co. Ltd. and Chugai U.S.A., Inc. is made in Japan through the use of host cells transformed or transfected with a DNA sequence encoding for EPO. (CX-85)

67. All EPO produced by Chugai and shipped to the United States has been produced with host cells having the human cDNA sequence. (RX-24 - Request for Admission No. 17).

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IV. ERYTHROPOIETIN

A. Erythropoietin Defined

71. Natural erythropoietin ("natural EPO") is a hormone made in the kidney of normal mammals that is released into the circulation and acts on the blood forming tissue, primarily the bone marrow, to regulate the rate at which red blood cells are formed. (Goldwasser, Tr. 7)

72. Red blood cells direct the supply of oxygen to the tissues through the body. Such cells are continuously growing old, dying and are replaced by new red blood cells formed primarily by the bone marrow. (CX-4C, at 2)

73. The process of red blood cell formation must be controlled precisely to ensure there is a proper number of red blood cells to carry oxygen efficiently. Too many red blood cells will impede circulation. A deficiency of red blood cells will result in anemia. (CX-4C, at 2)

74. Erythropoietin is an essential hormone for human health because it is the regulator of red blood cell production. (Goldwasser, Tr. 7)

B. Kidney Cells Are The Source of Natural Erythropoietin

75. The first paper describing a hormonal mediator of red blood cell formation in humans was published in 1906 by Paul Carnot and Camile Defandre in Paris. Carnot had originally called it "imatapoietin". In 1943, the existence of this material, which controlled production of red blood cells, was confirmed by Newton Krumdieck. By the late 40's and early 50's researchers were convinced such a material existed and controlled red blood cell formation. Messrs. Bonsdorff and Jalavisto of Finland are credited for naming the material erythropoietin, erythro meaning red, to signify the specificity of the material's action. (Goldwasser, Tr. 7-9)

76. In 1957, Dr. Jacobsen and his colleagues, among them Dr. Goldwasser, demonstrated that the human kidney was the source of human natural EPO production. By 1984, the actual location of the EPO producing cells in the kidney was still undetermined. (Eschbach, Tr. 544; CX-4C; Lin, Tr. 253; Sadler, Tr. 853)

77. Dr. Goldwasser is the former Chairman of the Department of Biochemistry and Molecular Biology at the University of Chicago. He received his Ph.D. in Biochemistry from the University of Chicago in 1950 and since that time has focused his research interests on studying the biochemistry of erythropoiesis, cell differentiation and hormone action - concentrating on the study of erythropoietin. (CX-4C, at 1-2)

78. The production of EPO by normal kidney cells is regulated by the level of oxygen circulating in the blood. A decrease in oxygen circulation triggers increased production of EPO. (Lin, Tr. 253)

79. Thus, EPO production by cells within the kidney of a normal person is a highly regulated process responsive to the level of oxygen in circulation. (Shoemaker, Tr. 1004-1005)

80. Dr. Goldwasser determined that persons with chronic kidney disease (i.e. chronic renal failure) were not producing enough erythropoietin to keep the supply of red blood cells at the appropriate level. Such persons suffer from anemia. (CX-4C, at 2)

81. **Anemia** refers to reduction in the number of red blood cells that are in the circulation. Anemia is defined by reference to a measure called the "hematocrit". Hematocrit refers to the volume of red blood cells compared to other blood components in a given volume of blood. In men, the normal hematocrit level is between 42 and 48, and in women between 38 and

43. Any hematocrit below these levels is defined as anemia. The hematocrit of a person who is suffering from the anemia of chronic renal failure would be between 15 and 30. (Eschbach, Tr. 540-541)

82. Prior to 1981, patients with the anemia of chronic renal failure were generally treated in one of two ways, depending on the severity of the anemia. Patients with severe anemia would either receive periodic blood transfusions to maintain them or were given androgen, or male hormone, therapy, which in some individuals stimulates the production of red cells. Other than these treatments, there was no treatment for anemia prior to 1981. (Eschbach, Tr. 542)

C. Isolation and Collection of Therapeutic Amounts of Natural EPO Proved Unsuccessful

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 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)

85. Dr. Goldwasser and others worked continuously from 1954 until 1971 to obtain samples of sheep EPO by purifying serum from sheep. The work resulted in obtaining a small amount, about 200 micrograms, of what was thought to be pure sheep EPO. This amount was sufficient to identify some of the chemical and biological properties of the material. (Goldwasser, Tr. 11; CX-4 at 3-4C)

86. In 1971-72, Dr. Goldwasser and Dr. Chiba, in Goldwasser's laboratory, worked on purification of human urinary EPO and discovered a way to inactivate certain enzymes which degraded EPO in urine. (CX-4C at 5)

87. Subsequently, in about 1975-76, Dr. Goldwasser, Dr. Kung, and Mr. Miyake, who had collected urine from patients with aplastic anemia, collaborated to separate and purify natural EPO from the urinary source. They succeeded in collecting an amount of highly purified, homogeneous natural EPO and published their procedure in 1977. (CX-4C at 5-6)

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)

91. Moreover, from the 1950's and into the 1980's many individuals in the field incorrectly postulated that there were substances in the blood of patients with kidney failure that would inhibit the action of EPO, blocking its effect on the production of red blood cells. The prevailing opinion was that EPO would be effective, if at all, only if given in large doses. (Eschbach, Tr. 545)

92. The question of whether mammals generated inhibitors that would render the use of natural EPO ineffective as a therapy was studied by Dr. Eschbach and Dr. Adamson. (Eschbach, Tr. 545)

93. Dr. Eschbach is a clinical professor of medicine at the University of Washington, specializing in the field of nephrology. Dr. Eschbach received his medical degree from Jefferson Medical College in Philadelphia, did his internship in medicine at King County Hospital in Seattle, and his internal medicine residency at the University of Washington and at Henry Ford Hospital in Detroit. Dr. Eschbach subsequently undertook a research fellowship in nephrology at the University of Washington. Dr. Eschbach has been involved in the discipline of nephrology for 25 years, and has taught and published numerous papers on the subject. He has lectured around the world on the subject of the anemia of chronic renal failure. Dr. Eschbach is qualified as an expert in the field of nephrology. (Eschbach, Tr. 535-538; CX-93)

94. Dr. Eschbach collaborates with Dr. John Adamson, head of the division of hematology at the University of Washington. (Eschbach, Tr. 539-540)

95. In 1969, Dr. Eschbach and Dr. Adamson initiated a study in anemic sheep. In the study, the investigators collected plasma rich in EPO from sheep which had been made anemic. The researchers subsequently infused this plasma into both normal sheep and sheep with kidney failure. The results demonstrated that the EPO-rich plasma stimulated red blood cell production identically in both types of sheep, demonstrating that there was no inhibition of the effect of the EPO in animals with chronic renal failure. Dr. Eschbach and Dr. Adamson first began to report these results at clinical meetings in 1981, and published the results in 1984. The experiments continued until 1983. (Eschbach, Tr. 545-546)

96. It was not until the results of Dr. Eschbach's research with animal models were published in 1984 that it was established that inhibitors, if there were any, probably would not in fact blunt, or inhibit the effect of EPO therapy. (Eschbach, Tr. 578).

97. Between 1981 and 1984, Dr. Eschbach also conducted a human experiment to confirm the results of the sheep model. In the human experiment, the researchers had the opportunity to obtain a small amount of EPO-rich human plasma, which was then infused into a patient suffering from chronic renal failure. Employing radioactive iron techniques, the researchers were able to demonstrate that the patient responded to the EPO in the plasma. However, the experiment was limited in scope and full scale clinical tests could not be conducted because of the lack of EPO rich human plasma. (Eschbach, Tr. 547)

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

D. Amgen's Recombinant EPO -
Amgen Was The First To Clone EPO

99. Dr. Eugene Goldwasser was approached by Dr. Salzer of Amgen in 1980 and he agreed to collaborate with Amgen in the EPO field. Goldwasser agreed to be a consultant to Amgen on all matters concerning EPO and to help out concerning the cloning of the EPO gene. (Goldwasser, Tr. 13).

100. In August of '81 there were only seven or eight people employed at Amgen. Dr. Lin was hired at that time by Amgen as a research scientist for no particular purpose. He chose the EPO project as his first research assignment from a number of available projects. (Lin, Tr. 389). His goal was to clone the human erythropoietin gene. (Lin, Tr. 234). Until Dr. Lin had cloned the EPO gene, only two persons worked on the EPO project at

Amgen: Dr. Lin and his assistant, C.H. Lin. (Lin, Tr. 241).

101. There was no source for recombinant EPO available prior to the fall of 1983. (Sadler, Tr. 842)

102. As a protein, EPO is made up of a series or chain of amino acids. (Goldwasser, Tr. 16)

103. Only some of the amino acid sequence of erythropoietin was known in 1982. (Ullrich, Tr. 669)

104. The gene for erythropoietin is essentially the set of instructions telling a cell how to make erythropoietin. (Goldwasser, Tr. 19-20)

105. There was no description of the correct structure of the erythropoietin gene prior to the fall of 1983. (Sadler, Tr. 842; Ullrich Tr. 669)

106. No one had reported the cloning of the erythropoietin gene prior to the fall of 1983. (Sadler, Tr. 842)

107. During the period 1982 to 1983, a cell that had been transformed or transfected with a DNA sequence coding for EPO did not exist. (Ullrich, Tr. 669)

108. In the 1982-83 time frame, very few proteins had been successfully produced by recombinant DNA techniques. (Ullrich, Tr. 671)

109. In sum, prior to the fall of 1983, no one had reported the cloning of the EPO gene, there was no source of recombinant EPO available and there was no available description of the correct structure of the EPO gene. (Sadler, Tr. 842)

110. The first successful cloning of the EPO gene was not reported to Dr. George Rathmann at Amgen until late in 1983. (Rathmann, Tr. 178).

111. In late 1983, Amgen first successfully cloned the EPO gene. (Rathmann, Tr. 178)

112. Amgen reported the cloning of the EPO gene to its Scientific Advisory Board prior to making a public announcement on December 12, 1983. (Rathmann, Tr. 178-180; CX-192)

113. On or about December 12, 1983, Amgen issued a press release that announced the cloning of the EPO gene by Amgen. (CX-192)

114. On page 744 of the 28 February - 6 March, 1985 issue of Nature, Amgen announced the availability of recombinant human EPO made by Amgen for research purposes. (Rathmann, Tr. 186-187 and 216-217; CPX-1; CX-20)

115. It was Genetics Institute, however, and not Amgen who was first to publish the erythropoietin amino acid and DNA sequences. (Rathmann, Tr. 210).

V. RECOMBINANT TECHNOLOGY IN GENERAL

A. Basic Steps In Protein Synthesis

116. Proteins are composed of amino acids. Amino acids are small molecules that are characterized by a certain composition and type of chemical bond. There are twenty amino acids that are commonly employed as building blocks of all proteins in the body. (Sadler, Tr. 763)

117. A "nucleic acid" can be either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA). (CPX-9 at 11)

118. Deoxyribonucleic acid ("DNA") is a double-strand molecule composed in part of nucleotides referred to as "C", "G", "T" and "A" (cytosine, guanine, thymine and adenine respectively). The order of these

nucleotides within the DNA stores the information of the genetic code. (Sadler, Tr. 776)

119. Within DNA, a "C" nucleotide on one strand always pairs with a "G" nucleotide on the other strand. A "T" nucleotide on one strand always pairs with an "A" nucleotide on the other strand. Thus the information content of one strand is complementary to the information of the other strand. (Sadler, Tr. 776)

120. DNA contains a sequence of the "C", "G", "T" and "A" nucleotides which, taken three at a time in triplets called "codons", provide a code through an intermediary nucleic acid, ribonucleic acid ("RNA") to establish the identification of an amino acid to be incorporated into a protein. (Goldwasser, Tr. 20)

121. The structure of all proteins made in all cells is derived from the information coded in the gene for that protein. The gene essentially is DNA in a particular order (the code) which instructs the cell to make the protein of the composition defined in the gene. There are perhaps several million genes and thousands of proteins in the cell, and each one is specified by a particular code in the genetic material. (Goldwasser, Tr. 19-20)

122. A protein can be characterized as a string of amino acids between two ends. The "left-hand end" of the amino acid sequence is referred to as the "N-terminal" sequence. This refers to the amino group (NH_2) at that particular end of the protein. The right hand end of the protein is referred to as the "C-terminal" because of the carboxyl group (COOH) at that end. (Lin, Tr. 281-283)

123. The process conducted by a cell in making a protein generally involves the cell reading instructions in the DNA, transcribing them into a working copy, which is the messenger RNA (mRNA), and then using the information in the mRNA to assemble the amino acids, one at a time, into the full amino acid sequence for that protein. The amino acid sequence comprises the primary structure of the protein. (Goldwasser, Tr. 20-21)

124. The terms, transcription, translation, glycosylation and secretion, describe in general terms some of the events that take place between the state of being DNA and the state of being a protein outside the cell. (Davies, Tr. 457)

1. <u>Transcription</u>

125. The first step in the cellular production of proteins is to convert a DNA sequence into RNA. The RNA sequence represents a portion of the DNA. This process is known as transcription. (Sadler, Tr. 772)

126. DNA is "read" by the transcription enzymes of the host cell, and transcribed into a sequence of ribonucleotides or RNA. (Sadler, Tr. 776)

127. The enzyme carrying out transcription is RNA polymerase. (CPX-9 at 41)

128. Natural genes as well as host cells contain promoters and sequences telling the gene when to start and stop transcription. These sequences are not unique to host cells. (Sadler, Tr. 869).

129. RNA, like DNA, is composed of nucleotides. The "T" nucleotide of DNA is replaced by a "U" (uracil) nucleotide in RNA. Thus, RNA is composed of "C", "G", "A" and "U" nucleotides. (Sadler, Tr. 776-777)

130. Sections of the genomic DNA are copied into the molecule known as messenger RNA, which transports the information stored in the genomic DNA

into other areas of the cell. The information stored in the mRNA then directs the construction of a protein, such as EPO, in the other areas of the cell. This protein then executes various functions in the body or in the cell that produced it. (Ullrich, Tr. 654)

131. Most human genes contain their coding sequences in small blocks of DNA referred to as "exons." Within an individual coding block, the exons will be broken by non-coding sequences referred to as "introns." The entire sequence will be transcribed into mRNA. Subsequently, the portions of the mRNA representing introns will be removed by a process called RNA splicing, which very precisely joins the remaining blocks of mRNA together in the proper coding sequence. Each triplet is thus maintained and can specify the appropriate amino acid. (Wall, Tr. 613)

132. Transcription of the DNA code to mRNA is a process that goes on in a recombinant cell and in all cells which express EPO or which are in the act or course of producing EPO. The process of transcription in the human kidney cell might not begin unless there is a signal from outside the cell. (Goldwasser, Tr. 59-60).

2. Translation

133. Ribosomes assist in the production of proteins by "reading" the code of an RNA molecule. The RNA is read in a series of ribonucleic acid triplets called codons. Each codon specifies a single amino acid in the protein. The order of the codons determines the sequence of amino acids in the protein. This process is known as translation. (Sadler, Tr. 772-773)

134. Because there are four possible nucleotides in RNA, there are 64 different possible codons or triplet combinations. However, there are only twenty amino acids. Thus, some amino acids are encoded by more than one

codon. This is referred to as redundancy or degeneracy in the genetic code. Also, three codons are reserved for termination of a protein. (Sadler, Tr. 778)

135. "Conservation" of proteins between species refers to the similarity of the amino acid sequence of that protein as produced by two different species. Perfect conservation would mean that the amino acid sequences of the two proteins were identical. (Ullrich, Tr. 714-715)

136. The degree of conservation of proteins between mammalian species is often high. However, some proteins exhibit very low conservation between species. (Ullrich, Tr. 714)

137. Ribosomes assemble amino acids in sequence to form a protein. (Sadler, Tr. 763-764)

138. In the process of translating a protein, the ribosome first finds a specific codon called an initiator codon. After the initiator codon, the ribosome continues to "read" the codons in the RNA. As each subsequent codon is read, the corresponding amino acid is attached to the peptide chain in the order specified by the codons. (Sadler, Tr. 778-779)

139. Transfer RNA (tRNA) is a special type of RNA which mediates the translation process. tRNA contains one region called the anti-codon which is complementary to a specific codon. Another region of the tRNA contains the amino acid that corresponds to that specific codon. (Sadler, Tr. 779)

140. Actual translation of amino acids occurs in the cytoplasm for both CHO cells and human kidney cells that produce EPO. (Goldwasser, Tr. 78-79).

141. The statement contained in the '008 patent that, "messenger RNA translation process involves the operation of small RNA strands called

tRNA which transports individual amino acids along the messenger RNA strand to allow for formation of polypeptide and proper amino acid sequences" describes briefly what occurs in a host cell which has been stably transformed or transfected with a DNA sequence and encoding erythropoietin. This statement also generally applies to what occurs in a human cell producing EPO. (Lin, Tr. 261-262. Lin Deposition RX-12C at 412).

142. The statement contained in the '008 patent that, "this messenger RNA translation process involves the operation of small RNA strands transfer RNA which transport and align individual amino acids along the messenger RNA strand to allow for formation of polypeptide in proper amino acid sequences" generally describes what occurs in the cells of the human kidney which produces EPO. (Lin, Tr. 263, Lin Deposition RX-12C at 415-416).

143. The statement contained in the '008 patent that "the messenger RNA message derived from DNA in providing the basis for the transfer RNA supply and orientation of any given one of the twenty amino acids for polypeptide expression is in the form of tryptic codons or sequential groupings of three nucleotide bases" applies to the cells of human kidneys which are producing EPO and also generally describes what occurs in a host cell containing a DNA sequence encoding for EPO. (Lin, Tr. 265, Lin Deposition RX-12C 416-417).

3. <u>Post Translation Processes</u>

144. After a protein is assembled by a ribosome, the protein folds to adopt a three-dimensional shape that is characteristic of the protein and permits it to perform its function within the cell. (Sadler, Tr. 764)

145. The phrase "folding of the protein" refers to a particular configuration that each protein assumes. The amino acids are joined, essentially like long beads on a string. Although the string is not infinitely flexible, it has a large number of configurations that it can assume. However, there is generally only one configuration that confers biological activity. There is no reliable information to indicate the mechanism that causes folding to the particular shape that confers biological activity to the molecule. Without the specific three dimensional shape conferred by folding, the molecule would not have a biological effect. (Goldwasser, Tr. 41-42)

146. Folding of the protein into a three dimensional shape necessary for the protein to be biologically active takes place in a recombinant cell and also in cells of the human body that are expressing EPO. (Goldwasser, Tr. 63, 79).

147. Subsequent to translation, disulfide bonds are formed between specific amino acids in the protein. (Sadler, Tr. 773)

148. Subsequent to translation, certain portions of the protein may be removed by the action of enzymes known as proteases. (Sadler, Tr. 773, 781)

149. Proteins destined for secretion from the cell, such as EPO, contain a sequence called a signal peptide which causes the protein to be directed to the endoplasmic reticulum. (Sadler, Tr. 773, 781)

150. At the endoplasmic reticulum, carbohydrate residues are added to specific sites on the polypeptide chain. This process is known as "glycosylation". Glycosylation occurs at sites having the amino acid residues asparagine, serine or threonine. (Sadler, Tr. 773, and 781-782)

151. The signal peptide is removed by a process called proteolytic processing. (Sadler, Tr. 781)

B. Construction Of A DNA Library

152. When you make a genomic DNA library the objective is to take the total DNA from a given organism, and divide it into small pieces and place them in individual phages, so you have a representation of the total genome of the organism in small fragments. (Davies, Tr. 475)

153. A library may only contain 80% of the DNA sequences, and the gene you are searching for may be in the missing 20%. (Davies, Tr. 475)

154. When a library is missing certain portions of the sequence, you go back and keep making libraries until you have libraries which are representative of every piece of DNA sequence which exists in the organism. (Davies, Tr. 475)

155. The Maniatis library is considered to be the first good human genomic library and is named after its creator, Dr. Maniatis from Harvard University. It is a standard library. (Davies, Tr. 505)

156. The Maniatis library is not complete, and if not kept properly, it degenerates. (Davies, Tr. 505)

157. The Maniatis Manual of Molecular Cloning was the only laboratory manual on cloning available in the early 1980s. The manual contains many mistakes and reflects the personal views of Dr. Maniatis. (Ullrich, Tr. 701-3)

158. Reverse transcriptase is now being used in the laboratory to create DNA from RNA. Such DNA is known as complementary DNA or cDNA. (Ullrich, Tr. 656)

159. Reverse transcriptase is produced by certain viruses, which store their genetic information as RNA rather than DNA. Cells store their genetic information as DNA. In order for the RNA viruses to take advantage of the cellular processes after they infect a cell, they must convert their genetic material to DNA. Reverse transcriptase performs this conversion. (Ullrich, Tr. 655-656)

160. cDNA, is assembled from mRNA molecules. In this process, an mRNA molecule is transcribed into a single strand of DNA by the enzyme reverse transcriptase which is isolated from certain viruses. A second enzyme then converts the single stranded DNA into a double stranded DNA molecule. This DNA is known as cDNA. (Sadler, Tr. 812-813)

161. cDNA is transcribed from mRNA after the mRNA splicing process. cDNA, unlike genomic DNA, contains no introns. (Wall, Tr. 612-614)

162. In making cDNA libraries, you must isolate the messenger RNA first and then convert the messenger RNA into its complementary DNA. (Davies, Tr. 475-476)

163. A cDNA library is made in the same manner as a gDNA library, but employs cDNA instead of gDNA. (Sadler, Tr. 811)

164. If the messenger RNA of interest is in very low concentrations, there is a possibility that when the cDNA library is made, the mRNA of interest will not be represented. (Davies, Tr. 476)

165. A library composed of genomic DNA is different from a library composed of complementary DNA. For example, gDNA libraries are approximately 100 times larger and more complex than cDNA libraries. For also gDNA includes DNA sequences called "introns" which complicate the identification of a gene because the introns are noncoding. There are

other noncoding sections of gDNA, such as promoters and repetitive sequences. The cDNA library, which is created from the mRNA, is much simpler because it includes only those DNA sequences that actually encode for proteins in the human body. (Lin, Tr. 285-289)

C. Screening Methods

166. The three general screening techniques that were used to clone genes in 1983 were (i) screening for the gene using specific oligonucleotide probes made with some knowledge of the protein structure, (ii) screening for the expression of a protein with the use of a specific antibody to that protein, and (iii) screening cDNA made from RNA that was a specific message for the desired protein. (Goldwasser, Tr. 35)

167. Purification of mRNA was not a practical alternative for attempting to isolate mammalian protein genes because RNA degrades very rapidly. (Ullrich, Tr. 705)

168. The process of cloning involves the identification of the unique DNA isolate among a large mixture by means of a probe. In the process of cloning a DNA gene encoding for a particular protein, the particular library, being either genomic or CDNA, is screened using oligonucleotide probes. These probes hybridize with complementary sequences on the DNA in the library that is being screened. (Sadler, Tr. 816-818).

169. "Oligonucleotide" refers to a short sequence of nucleotides, generally DNA nucleotides. The number of nucleotides is typically between 14 and 60 or 80. (Sadler, Tr. 804)

170. During 1981 and 1982, the mixed oligonucleotide probe technique was one method for identifying cDNA clones of low abundance mRNAs. Very few of the genes that were cloned by such techniques had an abundance of

less than 0.1% of the total population of mRNAs. Most genes that were cloned by this technique had very high abundance mRNAs. (Ullrich, Tr. 700)

171. In 1983 essentially two options were available for the construction of oligonucleotide probes. If only short and highly degenerate sections of the amino acid sequence of the protein in question were known, a researcher could generate a number of short probes, proposing all the possible nucleotide combinations or the known section of the protein. On the other hand, if the researcher had information concerning a longer, yet degenerate section of the protein, the researcher could make educated guesses as to the most likely nucleotide sequences that would be used in the DNA to code such an amino acid sequence. This information could be utilized to construct a single long probe which could possibly hybridize to the DNA sequence. (Sadler, Tr. 807-808)

172. Researchers construct oligonucleotide probes based on information concerning the supposed amino acid sequence of the protein. The task of constructing an appropriate probe is complicated by the fact that certain amino acids can be encoded by more than one "codon," a three-base sequence of nucleic acids. Using amino acids sequences found in the protein, researchers construct probes based upon the possible nucleotide sequences for that amino acid. Amino acids having a relatively large number of corresponding codons are referred to as being "highly degenerate." Thus, a string of highly degenerate amino acids requires a correspondingly large number of oligonucleotide probes to cover all the possible codons for each of the amino acids on that string. (Ullrich, Tr. 697-698)

173. Highly degenerate amino acid sequences require a large number of oligonucleotide probes to search for the gene that codes for that sequence. (Ullrich, Tr. 698)

174. In general the more probes you have the better chance you have of finding the gene. (Davies, Tr. 471)

175. However, use of a large number of probes substantially increases the likelihood that some of the probes will hybridize to other genes that happen to have one of those sequences in them, creating misleading false positives during screening. (Ullrich, Tr. 698)

176. Amino acid sequences that contain tryptophan are potentially useful for making oligonucleotide probes because tryptophan is encoded only by one codon. Twenty amino acids are found in proteins but these amino acids are encoded by 64 codons. Many of the amino acids are thus encoded by more than one codon, some by as many as six codons. This multiple coding of some amino acids is referred to as degeneracy. (Goldwasser, Tr. 57-58; and CPX-9 at 38)

177. Ordinarily you try to construct probes from different regions of the amino acid sequence. (Davies, Tr. 471)

178. Trypsin is an enzyme that breaks down proteins at specific areas of the protein to create smaller pieces. These "tryptic fragments" are separated form one another using chromatographic techniques. They represent, essentially, larger pieces than the individual amino acids of the protein and smaller pieces than the whole protein. Such fragments are useful in obtaining the primary structure of the protein, i.e., the amino acid sequence of the protein. (Goldwasser, Tr. 15-16)

179. A sequencing machine determines the amino acid sequence of the proteins. The machine will analyze the amino acid sequence starting at the first amino acid at the N-terminal of the protein. The machine identifies each amino acid using chromatography techniques, proceeding from the N-terminal region to the C-terminal region. (Lin, Tr. 307-310)

180. Northern blots can be used as a tool for identifying the sub-pools of probe pools which contain the best candidates for use as probes in screening a DNA library. This technique is extremely difficult. (Ullrich, Tr. 727)

181. "Subprobes" refers to the technique of dividing a pool of probes into two or more smaller pools. In some cases, but not in all cases, the use of subprobes may simplify the task of screening. (Ullrich, Tr. 728)

182. A "northern blot" hybridization experiment involves the separation by physical means of mRNA molecules from the other types of RNA molecules contained in the cell. The mRNA is sorted by size and adsorbed onto a carrier material filter. This filter is then utilized during hybridization procedures to identify the location of a specific mRNA within the population of mRNAs. (Ullrich, Tr. 727)

183. Hybridization is the process whereby radioactively labeled probe DNA is applied to mRNA or DNA which has been bound to nitrocellulose filters. This application is done in a manner allowing the probe to specifically anneal to the complementary segment of DNA or mRNA bound to the filter. Clones complementary to the probe will retain the radioactivity from the probe, and can be identified by scanning the filter for radioactive spots. (CPX-9 at 77)

184. The A-T nucleic acid bond has a much lower stability than the G-C nucleic acid bond. As a result, a researcher must be extremely cautious about the temperature utilized to wash away insignificant hybridizations after screening a library. Use of low stringency conditions may result in both a large number of false positives and a washing away of the true positive. (Ullrich, Tr. 699)

185. Screening a library is like a fishing expedition. The operation is determined successful only when the gene is found. (Davies, Tr. 476, 501)

D. Expression Of EPO From Host Cell

186. A host cell is a cell in which a particular gene, which is not normally resident in the cell has been inserted for the purpose of expressing the protein coded by the inserted gene. (Goldwasser, Tr. 36)

187. Chinese Hamster Ovary Cells (sometimes called CHO cells) are a type of mammalian cell. (Lin, Tr. 377)

188. The CHO cell is probably the one mammalian cell line which is best understood in terms of its properties with respect to cell culture, and its properties with respect to introduction of DNA. (Davies, Tr. 524)

189. The CHO cell was chosen as a host cell because it is well studied and grows well in cell cultures. (Davies, Tr. 523)

190. "Transformation" and "transfection" refer to the introduction of DNA or other genetic material into an intact cell, transformation referring to procaryotic cells and transfection referring to eucaryotic cells. (Ullrich, Tr. 672-673)

191. The DNA sequence in an expression vector requires the cellular environment to carry out the expression of protein. (Lin, Tr. 398)

192. For expression in the host cell, an expression vector must have certain sequences, including an "A-T-G" codon to signal the start of protein synthesis, and a stop codon to terminate protein synthesis. (Sadler, Tr. 787)

193. An expression vector must have a region called a "promoter" or "promoter enhancer" to which the host cell transcription enzymes combine and begin transcribing RNA. The DNA sequences contained in the expression vector may also contain a sequence called a poly A signal that instructs the host cell to cut the RNA at that point and attach a sequence consisting of hundreds of "A" bases. (Sadler, Tr. 787-788)

194. An essential feature of an expression vector for cloned DNA is its ability to replicate in bacteria. This is because researchers breed DNA in bacteria in order to obtain a large amount of the DNA sequence in question. (Sadler, Tr. 786)

195. Another essential feature of an expression vector is a mechanism to select for bacteria carrying the DNA sequence in question, and if possible, the ability to kill those bacteria which do not. This is commonly accomplished by providing a gene that encodes a resistance to a certain antibiotic, so that the bacteria which do not carry the DNA in question and the accompanying antibiotic resistant gene, will be killed by that antibiotic. (Sadler, Tr. 786)

196. A lambda vector contains the gDNA, along with its own lambda phage DNA. Upon infection, the vector injects the gDNA and its own lambda DNA into the bacterium. The infected bacterium has its processes diverted to the production of the bacteriophage particles that contain both lambda

phage genomic DNA and the DNA fragments from the original cells. The population of bacteriophage forms the gDNA library. (Sadler, Tr. 809-811.)

197. Stable transformation or transfection refers to a situation where the DNA contained in the expression vector is fully integrated into the DNA of the host cell. A transient transfection or transformation refers to a case where DNA arrives in the host cell nucleus but is not integrated into the host cell DNA. Expression in the latter case will decrease. (Sadler, Tr. 792-793)

198. A gene is known to be stably transformed or transfected when a cell, such as host CHO cell which is deficient in the enzyme DHFR (dihydrofolate reductase), is transfected with a DNA sequence vector which contains the human EPO gene and which also encodes the DHFR enzyme. Once the cell stably takes up this vector, it can then be grown in a medium which does not contain DHFR. (Lin, Tr. 396)

199. A host cell transfected with a purified and isolated DNA sequence encoding erythropoietin is the same as a host cell transfected with cloned DNA for erythropoietin. (Sadler, Tr. 860)

200. A CHO cell transfected with the DNA sequence encoding for EPO makes erythropoietin all the time and no signal is needed to begin production of erythropoietin. (Davies, Tr. 521)

E. The Recombinant Host Cell Has Qualitative Differences From The Human Cell That Produces EPO

201. The cell is basically a bag of cellular processes. (Lin, Tr. 405)

202. The host cell processes which allow the expression of EPO are an integral part of the cell. If the cell that is transformed or transfected with the gene produces EPO, one must assume that such processes are taking

place within the cell. If the cell does not produce EPO, it should be assumed that such processes are not occurring. (Ullrich, Tr. 676-677)

203. In comparing a hypothetical human kidney cell capable of and in fact producing erythropoietin and a recombinant CHO host cell producing recombinant erythropoietin, the two cells are very different. (Davies, Tr. 457-458)

204. One difference between the recombinant CHO cell and the human kidney cell is the placement of the promoter. Therefore the actual length of the messenger that is transcribed from this system may be different from the kidney cell. (Lin, Tr. 416-417; SPX-3; SPX-4)

205. The transcription start site in the CHO cell will be different from the natural kidney cell. (Lin, Tr. 418; SPX-3; SPX-4)

206. There are qualitative differences between the CHO cell and the kidney cell because the kidney cells make much less erythropoietin than CHO cells. (Lin, Tr. 418; SPX-3; SPX-4)

207. There are qualitative differences in the glycosylation process between the recombinant CHO cell and the natural kidney cell in the sugar levels that are added on to recombinant EPO as compared to natural EPO. (Lin, Tr. 423; SPX-3; SPX-4)

208. Although not entirely understood, there are some differences between the carbohydrate or sugar composition of EPO molecules from a CHO cell and urinary EPO molecules. (Lin, Tr. 430-432)

209. Because the natural kidney cell that makes erythropoietin has not been identified, it is not known what type of secretion mechanism is used by the natural kidney cell. (Lin, Tr. 424-425; SPX-3; SPX-4)

210. It is not known whether the secretion mechanism that is used by the CHO cell in secreting glycosylated erythropoietin is the same mechanism as that used for secretion by the natural kidney cell. (Lin, Tr. 425; SPX-3; SPX-4)

211. There is a difference in the biological activity of the recombinant erythropoietin as compared to the naturally occurring erythropoietin isolated from urine. It is not known whether the natural EPO circulating in the plasma has the same specific biological activity that urinary EPO has. (Goldwasser, Tr. 82-84)

212. Another difference between the human kidney cell and the recombinant CHO host cell which is of major significance with respect to the production of erythropoietin is that the CHO cell contains a human erythropoietin gene, a foreign gene, which directs the synthesis of erythropoietin. (Davies, Tr. 458)

213. Without the human erythropoietin gene the CHO cell is incapable of producing human erythropoietin. (Davies, Tr. 458)

214. The CHO cell does contain a gene for hamster erythropoietin but that gene is clearly not expressed by the cell. (Davies, Tr. 458)

215. In the case of the not yet identified human kidney cell which produces erythropoietin, it is known that the erythropoietin gene is on a particular section of Chromosome 7. However, in the CHO cell it is highly likely that the erythropoietin gene is somewhere totally different. It is somewhere in the genome surrounded by different regulatory elements than one would expect to find in the human cell. (Davies, Tr. 458-459)

216. When the foreign human EPO gene is placed in the CHO cell it is

unlikely to be in the same place in the CHO cell as it was in the human kidney cell. (Davies, Tr. 520)

217. The human EPO gene that is placed in the CHO cell is placed next to signals that do not regulate its expressions so that the gene is constantly turned on. (Davies, Tr. 524)

218. The processes in those two cells which are controlled by particular activators and controlling elements would be likely to be at the very least qualitatively different. Moreover, the regulatory functions within these cells would be different. (Davies, Tr. 459)

219. With respect to the four general process categories (transcription, translation, glycosylation and secretion) the interactions in the human kidney cell and the recombinant CHO cell would be different because the interactions are controlled by the particular proteins made by each type of cell. (Davies, Tr. 459)

220. The host cell for erythropoietin is characterized by the expression of the erythropoietin gene to an extent which ordinarily is not found in normal cells. (Goldwasser, Tr. 36)

221. Once one puts the human gene for EPO in a host cell, it is the combination of what is inside the cell plus the erythropoietin gene which allows one to make the product in such large amounts. (Davies, Tr. 526)

222. The CHO cell is a transformed cell line. It grow as a cell which is totally separate from its original tissue source. The kidney cell is in an organ, and interacts with other cells in that organ so the regulatory signals would be different. (Davies, Tr. 460)

223. The major quantitative difference between the two cells is that the CHO cell makes enormous amounts of erythropoietin without any signal.

The human kidney cell does not make erythropoietin unless it is triggered in some way. (Davies, Tr. 461-462)

224. Human kidney cells produce erythropoietin which can be isolated from human urine. The amount of erythropoietin that can be obtained from 10,000 liters of urine is definitely insufficient for therapeutic treatment. (Davies, Tr. 460)

225. Dr. Davies testified that the order of magnitude of the production of EPO by the CHO cell as compared to the kidney cell must be a thousand fold perhaps even a million fold. (Davies, Tr. 525)

226. The quantitative differences are the best example of the fact that the two cells are qualitatively different. (Davies, Tr. 462)

227. The fact that a greater amount of EPO is produced in the CHO cell is a quantitative difference that is based on qualitative changes in the cell. (Davies, Tr. 521)

228. Differences in the cell surface can be demonstrated to the extent that the cells respond to different receptacles. The translation apparatus of the two cells is different. The ribosomes of the hamster cell differs from the ribosomes of the human cell. The RNA polymerase which is responsible for transcription in the hamster cell is different from that of human cells, although the human polymerase has not been characterized in any great detail. (Davies, Tr. 461)

229. Dr. Davies does not consider SPX-3 and SPX-4, which were sketches drawn by Dr. Lin at the request of staff counsel, to be a fair representation of the human kidney cell producing erythropoietin and the recombinant CHO Cell producing recombinant erythropoietin. (Davies, Tr. 461; SPX-3; SPX-4)

230. SPX-3 and SPX-4 do not show the many components of the cells which are different. (Davies, Tr. 461; SPX-3; SPX-4)

231. Human kidney cells, when grown in cultures similar to those used with CHO cells, do not produce EPO. However, if such cells are transfected with a DNA sequence coding for EPO, the cells will produce human EPO. Such EPO will be produced in a different manner than the manner in which the non-transfected kidney cell would produce EPO. (Ullrich, Tr. 680)

232. The CHO cell conducts new and different processes after it is transfected with a DNA sequence coding for EPO. When a cell is transfected with any introduced gene, a new cell is created not only by virtue of having a new DNA sequence, but by the fact that the entire physiology of the cell is taken over and dominated by the presence of the introduced gene. The presence of the introduced gene, and its need to express its genetic information, influences the rest of the cell's characteristics, such that the cell is a different one than it was before. (Ullrich, Tr. 681)

233. In all human cells there are gene segments which are coded for erythropoietin but all human cells do not produce erythropoietin. The reason why all human cells do not produce erythropoietin is simply not known. (Sadler, Tr. 855)

VI. <u>THE LIN '008 PATENT</u>

A. <u>History Of The Patent</u>

234. U.S. Patent No. 4,703,008 issued on October 27, 1987. The '008 patent, which identifies Fu-Kuen Lin as the sole inventor, issued out of

U.S. Patent Application No. 675,298, which was filed on November 30, 1984. (CX-1)

235. Application No. 675,298 was a continuation-in-part application of U.S. Patent Application No. 561,024, which was filed on December 13, 1983, and a continuation-in-part application of U.S. Patent Application No. 582,185, which was filed on February 21, 1984, and a continuation-in-part application of U.S. Patent Application No. 655,841, which was filed on September 28 1984. (CX-1)

236. The '008 patent asserts an effective filing date under 35 U.S.C. Sec. 120 of December 13, 1983. (CX-1; and CX-2)

237. The face of the '008 patent indicates that Kirin-Amgen, Inc. is the assignee of the patent. However, the U.S. patent rights were assigned by Kirin-Amgen to Amgen. (CX-1; CX-169)

238. The specification of the '008 patent noted the prior art use of mixed probes. Specifically, the specification of the '008 patent noted, "Among the more significant recent advances in hybridization procedures for the screening of recombinant clones is the use of labeled mixed synthetic oligonucleotide probes, each of which is potentially the complete compliment of a specific DNA sequence in the hybridization sample including a heterogenous mixture of single stranded DNAs or RNAs. These procedures are acknowledged to be especially useful in the detection of cDNA clones derived from sources which provide extremely low amounts of mRNA sequences for the polypeptide of interest." (CX-1, col. 4, lines 17-27)

239. The specification of the '008 patent also noted the prior art use and availability of the "Maniatis library" of human genomic DNA. (CX-1, col. 4, lines 49-64)

B. Scope And Meaning Of Claims

240. Claim 1 of the '008 patent specifies the DNA sequences encoding erythropoietin which include the specific sequences set forth in figures 5 and 6 of the patent. (Lin, Tr. 379; CX-1)

241. Claim 1 could be interpreted to include a description of a DNA molecule which would have both an EPO coding sequence and a human EPO promoter. (Lin, Tr. 381-382; CX-1)

242. The language of Claim 1, however, does not necessarily require a human promoter. Under Claim 4 the cell can be constructed using EPO DNA sequences in such a way so as to allow expression. Certain constructions, however, may not allow efficient expression. (Lin, Tr. 381-382; CX-1)

243. Claim 2 of the '008 patent describes the coding sequence which will produce human EPO. (Wall, Tr. 610)

244. An isolated and purified human DNA sequence encoding EPO does not by itself produce EPO. (RX-24 - Request for Admission No. 18).

245. An isolated and purified human DNA sequence encoding EPO does not by itself perform a process. (RX-24 - Request for Admission No. 19).

246. Claim 4 in the '008 patent includes a transformed or transfected host cell which has only one copy of the EPO gene. (Lin, Tr. 387).

247. The language contained within claim 4, "in a manner allowing the host-cell to express erythropoietin" means that the cloned erythropoietin DNA must be in a suitable expression vector containing the elements required for transcription in the host cell chosen, whether it is a eucaryotic or procaryotic cell. (Sadler, Tr. 798).

248. From a molecular biology point of view the phrase "in a manner

allowing a host cell to express erythropoietin" is a description of the cell's capacity to produce erythropoietin. (Lin, Tr. 385; CX-1)

249. The language "in a manner allowing the host cell to express EPO" is descriptive of the property of a host cell. (Lin, Tr. 383-386, 408).

250. One skilled in molecular biology would understand claim 4 to describe a prokaryotic or eucaryotic host cell, containing a DNA sequence that would encode human erythropoietin, meaning a genomic DNA or CDNA clone encoding for human EPO. (Sadler, Tr. 798).

251. One skilled in molecular biology would view Claim 4 of the 008 patent to describe host cells into which the sequences of claim 2 have been introduced in a manner allowing them to express it. That is, the coding sequence is introduced with some sort of appropriate signal which would allow the DNA to be transcribed and various other processes that occur in the cell to ultimately express EPO. (Wall, Tr. 610; Lin, Tr. 393).

252. The host cell would have to be in an environment that includes certain protein factors, nutrients and amino acids in order for it to express EPO. In the absence of these nutrient factors there would not be any production of EPO. (Ullrich, Tr. 743-744; Wall, Tr. 637; Lin, Tr. 400-401; Shoemaker, Tr. 1018).

253. Claim 5 of the '008 patent is a claim to the carrier molecule which is used to introduce the cloned DNA sequence encoding for EPO into host cells. The expression vectors referred to are either a functional circular plasmid or viral DNA vector. (Wall, Tr. 610-611)

254. A vector or plasmid containing an isolated and purified human DNA sequence encoding for EPO does not by itself produce EPO. (RX-24 - Request for Admission No. 20).

255. A vector or plasmid containing an isolated and purified human DNA sequence encoding EPO does not by itself perform a process. (RX-24 - Request for Admission No. 21).

256. Claim 6 of the '008 patent refers to a stably transformed or transfected host cell. (Wall, Tr. 612)

257. In Dr. Sadler's opinion as a molecular biologist, neither claim 4 nor claim 6 describes a process; they describe a cell. (Sadler, Tr. 799).

258. Claim 7 of the '008 patent relates to the DNA sequence for the characteristics of EPO. (Lin, Tr. 394; CX-1)

259. Claim 7 of the '008 patent enlarges on the nature of EPO in relation to its biological activity. (Wall, Tr. 610)

260. Generally, a person skilled in the art of molecular biology would read claims 2 and 7 to describe a purified and isolated DNA sequence, i.e., a sequence that has been cloned free of other sequences. As recited in the claims, the DNA sequence consists essentially of a DNA sequence encoding human erythropoietin. Therefore it contains virtually the entire coding sequence for erythropoietin. Claim 7 modifies claim 2 somewhat so that it would include a DNA sequence that encoded a protein having much of the biological activity of erythropoietin but wouldn't necessarily have to be erythropoietin precisely as it exists in nature. (Shoemaker 1014; Wall, Tr. 602-609; Lin, Tr. 392-394; Sadler, Tr. 797, 799-800).

261. One skilled in the art of molecular biology would not view claim 2 or claim 7 of the '008 patent as claims directed to any processes. Claims 2 and claim 7 relate to isolated DNA sequences. (Shoemaker, Tr. 1014-1015).

262. Claim 23 of the '008 patent incorporates Claim 7 by reference. (Wall, Tr. 606)

263. Claim 23 describes the cell and gene together in the proper environment. The cell and the gene are an inseparable entity. (Lin, Tr. 400)

264. The language contained within claim 23, "in a manner allowing the host cell to express said polypeptide" relates to a capacity of the host cell and the structure of how the host cell is constructed. The host cell is constructed in such a way that it must have the gene put into it in a certain way and the gene must be constructed in a certain way so that the host cell will be able to express erythropoietin. Thus, this language explains part of the structure. (Rzucidlo, Tr. 1074).

265. The language contained within claim 23 "in a manner allowing the host cell to express said polypeptide" is functional language sometimes contained in patent claims. (Rzucidlo, Tr. 1075).

266. One skilled in molecular biology would view Claim 23 as one directed to a host cell which has a coding sequence introduced into it in such a way, with appropriate control signals, that the host cell is capable of expressing a peptide with the activity of EPO. (Wall, Tr. 606; Lin, Tr. 404).

267. A claim which includes a functional phrase does not actually claim the function described by that phrase. Thus the functions described by the language contained in claims 4 and 23, "in a manner allowing the host cell to express erythropoietin are not actually claimed by claims 4 and 23. Those functional phrases indicate a capability of the cell and how it is constructed. (Rzucidlo, Tr. 1194-1195).

268. The claims in the '008 patent, specifically claim 23, do not mention any culturing conditions. All the conditions which are necessary for the host cell to produce erythropoietin are already in the art. (Lin, Tr. 386, 403-404).

269. Claim 24 of the '008 patent builds upon Claim 23. (Wall, Tr. 607)

270. One skilled in molecular biology would view Claim 24 as relating to a transformed or transfected cell capable of producing EPO which is glycosylated. (Wall, Tr. 607; Sadler, Tr. 800-801).

271. Claim 25 of the '008 patent incorporates Claim 24. (Wall, Tr. 608)

272. Claim 25 refers more narrowly to a specific kind or eucaryotic cell, one derived from a mammal that can glycosylate erythropoietin when it is expressed from a vector that contains a DNA sequence according to claim 7. (Sadler, Tr. 801; Wall, Tr. 608).

273. Claim 27 of the '008 patent incorporates by reference Claims 25, 24, 23, and 7 of the '008 patent. (Wall, Tr. 609)

274. One skilled in molecular biology would view claim 27 as one relating to a host cell as in Claim 25 where the cell is a chinese hamster ovary cell. (Wall, Tr. 609; Sadler, Tr. 801).

275. Claim 28 of the '008 patent refers to a vector including a DNA sequence according to claim 7.

276. One skilled in the art of molecular biology would view claims 5 and 28 to describe biologically functional circular plasmids, i.e., expression vectors that contain the necessary DNA functions that would permit it to be utilized by the cell to produce erythropoietin. One

skilled in the art of molecular biology would not believe that any processes were covered by claims 5 or 28, in that they are directed solely to vectors used in the transfection of host cells. (Shoemaker, Tr. 1015-1016; Sadler, Tr. 866; Wall, Tr. 610-611; Lin, Tr. 393).

277. Claim 29 of the 008 patent refers to a host cell which is stably transformed and which includes the vector with the EPO sequence. (Wall, Tr. 615; Sadler, Tr. 802).

278. Claims 2, 4-7, 23-25 and 27-29 of the '008 patent claim genetically engineered host cells, vectors, and DNA sequences used to make recombinant erythropoietin. (RX-24 - Request for Admission No. 35). (Rzucidlo, Tr. 1068; Wall, Tr. 602-615).

279. In the '008 patent, claims 7, 23, 24, 25, and 27 each depend on the prior claim. (Wall, Tr. 604)

280. None of the claims of the '008 patent require that the host cell described be constitutively on. (Sadler, Tr. 803).

281. After a review of the '008 patent disclosure, including the claims and the specification, Dr. Sadler testified that, as a molecular biologist, he did not understand claims 4, 6, 23, 24, 25, 27, and 29 to be describing processes of any kind. (Sadler, Tr. 802).

282. One skilled in the art of molecular biology would view claims 4, 6, 23-25, 27 and 29 to describe host cells in which the host cell is transfected in a manner which allows the host cell to express erythropoietin. (Shoemaker, Tr. 1017).

283. The '008 patent specification does not contain any description of the specific steps or the specific processes that might occur in the cell itself when it produces erythr ietin. There is no description in the

application of any intracellular processes specifically and it was never discussed during the proceedings in the Patent Office.
(Rzucidlo, Tr. 1180-1181).

284. Robert Weist, general counsel for Amgen and an experienced patent practitioner stated in a public announcement regarding the '008 patent that "The patent will cover gene sequences encoding for erythropoietin as well as various vectors and cell lines used in the production of recombinant erythropoietin and should enable Amgen to establish a formidable position against any potential competitors." In the announcement Mr. Weist did not assert that the '008 patent covers processes of any kind. (RX 83, Rathmann, Tr. 202-203).

C. Intracellular Processes

285. The environment within a cell with regard to its intracellular processes is a dynamic one with many molecules moving from place to place and conditions of the cell being changed by the different conditions of the culture. When the recombinant host cell express erythropoietin there are processes going on within the cell. (Sadler, Tr 859)

286. A vast number of intracellular processes are performed when a host cell makes erythropoietin. These processes are integrated into the cell. These processes cannot be separated from the host cell if the cell is to make a useful quantity of erythropoietin. There are a few processes that can be separated from the cell, but the totality of the processes is much greater than the sum of the few parts that we understand.
(Goldwasser, Tr. 37-38)

287. The processes which occur within a host cell are considerably different from the processes which occur within a normal human kidney cell

which produces erythropoietin. The kidney cell produces erythropoietin in a highly regulated fashion, by increasing or decreasing the rate of synthesis of erythropoietin depending on the amount of oxygen in the circulatory system. The host cell carrying the amplified erythropoietin gene is unregulated. It produces erythropoietin in large amounts and at an uncontrolled rate. A recombinant host cell produces erythropoietin at a rate at least a million times greater than a human kidney cell. (Goldwasser, Tr. 38-40)

288. The processes that occur within a cell which result in the expression of erythropoietin are the basic processes of transcription, translation, glycosylation and secretion. (Shoemaker, Tr. 1019; Ullrich, Tr. 747; Lin, Tr. 407, 409-410).

289. In order for intracellular processes to work properly, they must occur within the cell. The processes which are separable from the cell are incapable of producing EPO in useful amounts. (Wall, Tr. 620)

290. The synthesis of a protein in a cell involves certain processes that are known in the general sense. The DNA code is transcribed to mRNA in the nucleus. The mRNA is translated. The message, or mRNA is translated by the ribosomes, from a ribonucleic acid sequence to an amino acid sequence. The protein is then folded into a three-dimensional shape and glycosylated in the cell. In the general sense, these procedures occur in both normal adult human cells that make erythropoietin and recombinant cells that make erythropoietin. However, the details of these intracellular processes may not be the same as between normal adult human kidney cells and recombinant host cells. (Goldwasser, Tr. 59-64)

291. RNA polymerase is different in a CHO cell as compared to a human kidney cell. This can be detected by electrophoresis. Electrophoresis indicates differences in amino acids, as indicated by differences in molecular weight. (Davies, Tr. 522-523)

292. Some of the processes a recombinant host cell performs to make EPO are known and some are not known. What is known relates to the transcription of the EPO gene to the messenger RNA ("mRNA".) The mechanism of transport of the message from the nucleus to the cytoplasm is not understood at all. Scientists do not understand very much of the processing of the mRNA to a translatable message. As to the translation of the mRNA on the ribosome system in the endoplasmic reticulum of the cell, some aspects are moderately well understood and some aspects are not well understood at all. Similarly, the mechanism which regulates the folding of the protein to its appropriate three-dimensional shape which will confer biological activity is not understood. (Goldwasser, Tr. 40-41)

293. The processes responsible for the making of erythropoietin by a host cell are not fully understood, have not been identified, and cannot be fully described. The best proof that a cell having a DNA sequence encoding for EPO is in fact performing the processes that make EPO is the existence of the end product with biological activity equivalent to that of natural EPO. That a host cell produce EPO in greatly different amounts is also evidence that the cell performs its processes in a very different manner than a natural cell. (Goldwasser, Tr. 42-44)

294. These processes that make EPO are inseparable from the host cell; they cannot be practiced outside of the host cell; without the host cell, there is no process. (Lin, Tr. 251)

295. In the recombinant host cells that express EPO, the human EPO gene which has been inserted into the cell presides over the processes that make EPO. (Lin, Tr. 250-251)

296. The general terms applied to intracellular processes, i.e., transcription, translation, glycosylation, and secretion, apply to the intracellular processes of both recombinant cells and normal cells, but the context of the terms is different. (Lin, Tr. 253-254)

297. The actual intracellular processes that are encompassed by the general terms differ in the two types of cells. (Lin, Tr. 259-260)

298. The processes for producing erythropoietin in recombinant host cells are apparently different than the processes for producing EPO in normal kidney cells. (Lin, Tr. 252)

299. The combination of processes that exist within the recombinant host cell are both qualitatively and quantitatively different from the processes that occur within a human kidney cell during the production of EPO. (Wall, Tr. 621)

300. In a host cell, there is an artificial promoter, which has been inserted into the host cell utilizing recombinant DNA techniques. In the normal human kidney cell, there is no such identifiable promoter. Consequently, the mechanism of activating the expression of erythropoietin may be considerably different in the two cells. (Goldwasser, Tr. 65)

301. Because the SV-40 promoter in the recombinant EPO gene is a far more effective promoter than the natural promoter of an unmodified EPO gene, recombinant cells are regulated in a different manner than normal human cells. (Lin, Tr. 255-256 and 270-271)

302. The SV-40 promoter existed before the invention and is not asserted to be conceived by Dr. Lin. (Lin, Tr. 279)

303. There are differences in the regulating states of recombinant host cells and normal human kidney cells. There are also differences in the location and integration of EPO genes in the two types of cells. (Wall, Tr. 621)

304. Recombinant host cells and normal human kidney cells differ in the protein factors in the nuclei of the cells which regulate the expression of the EPO gene. "Chromatin structures" are large complexes of both protein and DNA. The highly expressed gene will be in a very open chromatin structure, where the rarely expressed gene would be in a closed chromatin structure, inaccessible to enzymes. In a human kidney cell, the gene regulating the production of EPO is probably in a closed chromatin structure and not accessible to the transcriptional machinery, regulatory factors and polymerases which produce mRNA for EPO. This explains the low rate of production of EPO in normal human kidney cells. In the recombinant host cells, the EPO gene is readily accessible to enzymes, resulting in a high level of production of mRNA coding for EPO. (Wall, Tr. 621-623)

305. In the recombinant host cells, a gene coding an enzyme known as dihydrofolate reductase has been introduced along with the gene coding EPO. This gene, and anything linked to it, including the EPO gene, can be amplified under proper conditions such that the recombinant host cell may have hundreds of copies of the EPO gene. These copies could contribute significantly to the increased rate of production of EPO seen in the host cell. In contrast, the kidney cell contains only a single copy of the EPO gene. (Wall, Tr. 623-624)

D. <u>The Patent Office History</u>

306. The original patent application filed in the patent office contained a number of claims directed to different subject matter. The patent application contained claims directed to polypeptides, host cells, DNA sequences and vectors including the DNA sequences. In addition, the application as filed contained Claim 50. Claim 50 was a process claim, a process for the production of a polypeptide. The process consisted of growing a host cell which contained the particular DNA vector and then isolating the peptide from the growth media. (Rzucidlo, Tr. 1077-1079); CX-2, pp. 101-109.

307. Claim 50, directed to a process of producing the erythropoietin polypeptide, was recited in the form of steps:

1. the process of growing the host cell; and
2. the isolation of the polypeptide.

Thus, the process contained within claim 50 was a process wherein one grows a host cell and then isolates the polypeptide. (Rzucidlo, Tr. 1080); CX-2, p. 107.

308. In the original patent application which resulted in the '008 patent, there were also claims 56-60 which were process claims directed to a method for providing EPO therapy to a mammal. All of these process claims were written in the form of steps using words such as employing, treating etc., i.e. traditional process claims. (Rzucidlo, Tr. 1081); CX-2, p. 108.

309. In a preliminary amendment dated April 24, 1986, certain claims were added to the patent application and other claims were cancelled. The original process claim, claim 50, present in the original patent

application, was rewritten as claims 69-72. Claims 69-72 were directed to the process for the production of polypeptides. All of these claims recited the same procedure, i.e., growing a host cell and isolating the polypeptide. (Rzucidlo, Tr. 1086-1087); CX-2, p. 140-142.

310. In a preliminary amendment dated April 24, 1986 the applicant provisionally elected prosecution of those claims which are numbered 14, 15, 17 through 36, 58, and 61-72. The applicant characterized these claims as directed to "DNA sequences, vectors including DNA sequences, host cells transformed or transfected with the claimed vectors, and processes for the production of polypeptides through the use of claimed transformed or transfected hosts". Those claims that were withdrawn were not examined. The election was made "without traverse" meaning that the applicant relinquished any right to object to this election. The claims that are not elected are withdrawn from consideration by the examiner. (Rzucidlo, Tr. 1088-1087); CX-2, p. 143.

311. Of the claims that were elected for examination, Claims 69-72 were directed to processes for the production of polypeptides. (Rzucidlo, Tr. 1088); CX-2, p. 143.

312. In a declaration accompanying a petition to make special filed simultaneously with the preliminary amendment of April 24, 1986, the applicant characterized the remaining claims of the application as being directed to DNA sequences and to uses of the sequences for the large scale production of EPO. Later on, the applicant differentiated between what is claimed in claim 64 as referring to transformed or transfected host cells, and what is claimed in claim 70 as production processes. (Rzucidlo, Tr. 1090-1091); CX-2, pp. 180-184.

313. In an office action dated 6/16/86, the Examiner indicated that claims 1-13, 16, 37-39 and 59-60 had been withdrawn from consideration by the applicant. Amongst the claims withdrawn from consideration were claims to the final product erythropoietin. The elected claims constituted claims only to the DNA sequences, the vectors, the host cell and the process of making EPO using the host cell. In this action, the Examiner required restriction and delineated various groups of claims as reciting separate and distinct inventions. Group II included claims 14, 15, 17-36, 58 and 61-72, which were the claims provisionally elected by the applicant in the preliminary amendment. The Examiner then rejected claims 14, 15, 17-36, 58 and 61-72 on various grounds. (Rzucidlo, Tr. 1093-1094); CX-2, pp. 208-209.

314. The applicant responded to the Examiner's office action in a paper entitled "Applicants Amendment and Reply Under 35 U.S.C. §§ 1.111 and 1.115" dated October 3, 1986. In that response, the applicant amended claim 14 which was directed to DNA sequences. The claim was amended to indicate that the DNA sequence was one which was "purified and isolated". This claim was amended in such a manner in order to overcome the Examiner's rejection that without this language the claim read on a product of nature. To avoid that rejection, the applicant added the terms" purified and isolated." The same amendment was made to claim 34. (Rzucidlo, Tr. 1094-1096); CX-2, pp. 236-238.

315. In the applicant's amendment and reply filed October 3, 1986, the applicant once again characterized the claims remaining in the application as those that are "accordingly directed to DNA sequences, DNA vectors, transformed and transfected host cells and processes for the use of these

materials in the preparation of erythropoietin products...." (Rzucidlo, Tr. 1097); CX-2, p. 239.

316. Nowhere in the applicant's October 3, 1986 amendment and reply did the applicant attempt to distinguish the host cell claimed in its application on the basis of novel intracellular processes carried out in the host cell. (Rzucidlo, Tr. 1097-1098).

317. In an office action dated 2/5/87, the Examiner once again rejected all the claims that were elected on a number of statutory grounds, including 35 U.S.C. §§ 102 and 103. The bases for rejection of the process claims, claims 69-72, included 35 U.S.C. §§ 102, and 103. (Rzucidlo, Tr. 1098-1099).

318. The basis of the rejection was that it would have been obvious to express the erythropoietin gene sequence by using the EPO sequence in the expression plasmid disclosed in the Talmadge reference. In addition, the Examiner rejected claims 69-72 under section 102 as being anticipated by Talmadge on the ground that Talmadge discloses the expression of a mammalian protein using recombinant DNA transformed microorganisms. The claims were thus deemed to embrace the DNA sequences and protein expression methods of Talmadge. Further in considering the rejection of the process claims, the examiner stated that the process which was recited in those claims was an obvious process and that such claims were not patentable based on the appeals court decision in In re Durden, 226 U.S.P.Q. 359 (Fed. Cir. 1985) (Rzucidlo, Tr. 1101-1102); CX-2, p. 335-336.

319. In rejecting process claims 69-72 on the basis of 35 U.S.C. § 102 the examiner regarded the process claims as reciting nothing more or less than what happens each and every time a cell grows and expresses a protein.

The examiner believed that the process of claims 69-72 was the same process occurring in the cells described by Talmadge, and that the cells were expressing in the same way as the Talmadge cells were expressing. (Rzucidlo, Tr. 1102-1103).

320. In rejecting claims 69-72 under 35 U.S.C. § 103 the examiner stated that the process steps were exactly the same regardless of what the starting materials in the procedures were. Although the Talmadge reference referred to a different DNA sequence, a different host cell and expression of a different material, the basic process of expressing and isolating polypeptides was the same. Therefore the claims were rejected on the authority of the Durden decision. (Rzucidlo, Tr. 1103); CX-2, p. 336.

321. On 3/4/87, the examiner conducted an interview with the applicants. In a summary of that interview, the examiner stated that his "Durden position" was to be maintained. The Examiner affirmed his position that the process claims 69-72 would have been obvious to persons of ordinary skill in the art within the meaning of 35 U.S.C. § 103. (Rzucidlo, Tr. 1107); CX-2, p. 339 (Respondent's Exhibit 24 - Request For Admission No. 30).

322. In response to the office action of 2/5/87, the applicant filed an amendment and reply paper on March 12, 1987. In this amendment and reply, Amgen cancelled claims 14, 15, 17-36, 58 and 61-72. So all of those claims were deleted from the application including the process claims 69-72. Amgen then added new claims 73 to 103. The applicant stated, "applicant notes that none of the claims whose entry sought correspond to claims 69-72." (Rzucidlo, Tr. 1111) (Respondent's Exhibit 24 - Request For Admission No. 33); CX-2, pp. 341-347.

323. In the amendment and reply of March 12, 1987, the applicant stated that: "claims remaining in this application relate to DNA sequences, DNA vectors, transformed and transfected host cells useful in the preparation of erythropoietin products including, for e.g., polypeptide analogs of erythropoietin". (Rzucidlo, Tr. 1111-1112); CX-2, p. 367.

324. Upon cancelling process claims 69-72, the applicant further indicated that the "issues raised by the rejection are no longer present in the application". (Rzucidlo, Tr. 1119; CX-2, p. 367 (Respondent's Exhibit 24 - Request For Admission No. 34); Rathmann, Tr. 206-207).

325. Subsequent to the cancellation of the process claims, the applicant amended some claims and changed other claims. However, none of the claims subsequently added or amended included any process claims. (Rzucidlo, Tr. 1120).

326. On July 13, 1987, the applicant submitted another amendment and reply. Once again the applicant presented a chart comparing cancelled claims and resubmitted claims and made certain remarks in the amendment. This amendment represents all the claims that eventually issued in the application. The table indicates that there are no claims corresponding to the cancelled process claims present in the application. There is no indication that process claims 69-72 were being resurrected. The applicant characterized the claimed subject matter remaining in the application as relating to DNA sequences, DNA vectors, transformed and transfected host cells...." (Rzucidlo, Tr. 1120-1121); CX-2, pp. 430-439.

327. Claim 70 of the '008 patent included the step of growing under suitable nutrient conditions the prokaryotic or eucaryotic host cells transformed or transfected with the DNA vector according to claim 63.

Involved as part of that step is the intracellular processes carried out by the host cell. (Wall, Tr. 639).

328. When the '008 patent application was filed in the patent office, the Examiner in charge of the application classified the case in classification 435-68 which corresponded to the process for making a polypeptide using a DNA sequence. After the proceedings in the patent office were finished and the Examiner was making his final determination, he did a final interference search. The search included the area of class 435 but did not include sub-class 68, the process area in which the patent was originally classified. (Rzucidlo, Tr. 1084-1085, 1147).

VII. PATENT VALIDITY

A. Obviousness

1. Dr. Lin's Work on Amgen's EPO Project

329. Prior to joining Amgen, Dr. Lin received a Ph.D. in Biochemistry from the University of Illinois in 1971. Dr. Lin performed post-doctoral research work on cancer at both Purdue University and the University of Nebraska. Dr. Lin subsequently researched fungi physiology at the Institute of Botany, Academia Sinica in Taiwan. After returning to the United States, Dr. Lin performed microbiology research at Louisiana State University relating to the sequencing of tRNA, as well as the aging mechanism in human cells. After completing these studies, Dr. Lin performed research at the University of South Carolina on cloning the gene for globin, a gene involved in the synthesis of hemoglobin and red blood cell production. (Lin, Tr. 228-233; CX-91C)

330. Dr. Lin's first assignment at Amgen was to solve the problem of cloning the gene encoding for erythropoietin. (Rathmann, Tr. 173; Lin. Tr. 234; CX-91C)

331. Dr. Lin generally worked alone at the beginning of the EPO project. After approximately four or five months, he hired one associate. (Lin, Tr. 241)

332. Amgen was a very active company at this time, with a number of different projects under way, and new employees being hired. (Lin, Tr. 242)

333. Initial results from the EPO project were not encouraging. Other scientists at Amgen were reluctant to become involved in the project. (Lin, Tr. 240-241)

334. Amgen considered termination of the EPO project on several occasions due to the substantial difficulty in successfully cloning the EPO gene. (Rathmann, Tr. 181)

335. At one point, Dr. Rathmann placed a deadline on the EPO program after which it would be terminated if unsuccessful, however, the project did keep going and eventually was successful. (Rathmann, Tr. 181-182)

336. The EPO project at Amgen involved a number of tasks. Obtaining the protein, sequencing the protein, obtaining cells with mRNA that encoded for erythropoietin, and obtaining the antibody that could be used as a screening process or analytical reagent were some of the projects involved. (Lin, Tr. 234; CX-91C)

337. The goal of the EPO project was to clone the gene and insert it into a host cell so as to express significant amounts of EPO. Such quantities of EPO could be used in research and in the clinical setting to

test the therapeutic value of the protein in treating people with anemia. (Lin, Tr. 234-235)

338. Dr. Lin took a number of approaches in his attempt to successfully clone the EPO gene. Dr. Lin attempted to obtain samples of the EPO protein in order to analyze the amino acid sequence of the protein, and thus to gain insights into the structure of the gene itself. He tried to isolate cells which expressed EPO in enriched amounts, in hopes of obtaining mRNA for EPO, because it would then be easier to isolate the gene coding for EPO. Dr. Lin attempted to develop antibodies which would recognize EPO to use as a reagent or for screening. Dr. Lin also developed a model system based upon the betaglobin gene in order to analyze the hybridization conditions under which DNA probes would bind to the EPO DNA sequence. (Lin, Tr. 234-239; CX-91C)

339. When Dr. Lin joined Amgen in 1981, a sequence of approximately 20 amino acids had apparently already been identified near the N-terminal of the EPO protein. (Lin, Tr. 282-283)

340. By September, 1981, Dr. Lin had set out designing radiolabeled DNA probe sequences that might serve to identify the gene encoding for erythropoietin. (CX-91)

341. This N-terminal amino acid sequence information which Dr. Lin had prior to September of 1983 was incorrect, but Dr. Lin was not aware of the inaccuracy at the time. (Lin, Tr. 302-303)

342. Dr. Lin's initial techniques in 1981 were not successful in isolating the EPO gene. These techniques utilized information available to Dr. Lin describing the N-terminal amino acid sequence of EPO. (Lin, Tr. 289)

343. For approximately the next two years, Dr. Lin had oligonucleotide probes prepared based upon the available amino acid sequence information that was known. However, Dr. Lin was not successful in using those probes to isolate the EPO gene from human genomic libraries. (CX-91 at 3)

344. By late 1982, Dr. Lin determined that the amino acid sequence information for the N-terminal region of EPO obtained in 1981 and used to prepare oligonucleotide probes was incorrect. (Lin, Tr. 292-295)

345. From the beginning of the EPO project, Dr. Lin recognized the desirability of having additional amino acid sequences of EPO. (Lin, Tr. 290-291)

346. Dr. Lin believed that additional EPO would be helpful for determining the correct amino acid sequence of EPO, and also for making reagent antibodies, and to characterize the protein in the cells. (Lin, Tr. 301)

347. Dr. Lin also knew that in order to correctly design oligonucleotide probes with which to screen a DNA library, it was important to have correct information concerning the amino acid sequence of the protein in question. (Lin, Tr. 283)

348. Dr. Lin preferred to have amino acid sequence information on EPO from regions other than simply the N-terminal region. It was desirable to have amino acid sequence information from different regions in order to more effectively design oligonucleotide probes. (Lin, Tr. 301-302)

349. Information concerning the amino acid sequence of EPO was important to Dr. Lin's project. Without sequencing information, Dr. Lin would not have been able to design the correct probes to isolate the EPO gene. However, Dr. Lin could not know when designing a probe, i.e., in

advance of using it, whether a particular probe would work. He had to use whatever amino acid sequence information was available to make probes. (Lin, Tr. 310-312)

350. Sequencing of amino acids is performed on a machine. Dr. Lin was not involved in the development of the machine. The machine employed by Amgen was a prototype. (Lin, Tr. 306-307)

351. Dr. Lin never operated the sequencing apparatus at Amgen, nor did he give instructions as to how the sequencing work was to be performed. Sequencing was performed by the personnel in Dr. Lai's group. (Lin, Tr. 309)

352. In the early 1980's, purified EPO was extremely scarce. In addition to contacting Dr. Goldwasser, Amgen sought to obtain additional EPO from Toyobo and Dow for research purposes. (Rathmann, Tr. 212-213)

353. Toyobo eventually supplied Amgen with such material. Amgen also approached Dow as a source of EPO. Amgen also obtained EPO from Peter Duke. (Lin, Tr. 300)

354. For two years, Amgen sought to obtain more EPO for research purposes, including sequencing, from every possible source. (Lin, Tr. 301)

355. In late 1982 and early 1983, Dr. Lin sought additional samples of purified EPO from Dr. Goldwasser for use in his research. Dr. Goldwasser did not provide these samples until after January of 1983. (Lin, Tr. 295-296)

356. On or about August 30, 1983, Amgen received tryptic fragments of EPO from Dr. Goldwasser. (Lin. Tr. 304 and 329)

357. As of August 1983, when tryptic digest fragments of human EPO were received from Dr. Goldwasser, Dr. Lin needed to have more amino acid

sequence information in order to prepare suitable probes for regions other than the N-terminal of the protein. (Lin, Tr. 304)

358. Two pools of oligonucleotide probes, referred to as "EPV" and "EPQ", were prepared using information derived from the tryptic fragments of EPO supplied by Dr. Goldwasser. (Lin, Tr. 329-331)

359. Dr. Lin designed and ordered, but did not personally construct the EPV and EPQ oligonucleotide probes utilized in his project. (Lin, Tr. 311-313)

360. Dr. Lin ordered the EPV probes on September 2, 1983, and the EPQ probes on September 14, 1983. (Lin, Tr. 244; CX-60; CX-129C)

361. Dr. Lin's successful isolation and purification of the EPO gene occurred using the EPV and EPQ probes. (Lin, Tr. 331-333)

362. The human EPO fragments supplied by Dr. Goldwasser are identified in the '008 patent in Table 1 and at Column 1, lines 49-60. (Lin, Tr. 303)

363. Because tryptophan has only one codon, fragments that contain tryptophan can be helpful in designing oligonucleotide probes. If the neighboring amino acids are highly degenerate, however, then the value of having tryptophan is lessened. (Lin, Tr. 363)

364. After receiving the sequences from Dr. Lai for fragments 35 and 38, Dr. Lin specified the two mixtures of probes, the EPV and the EPQ mixtures. (Lin, Tr. 364)

365. Dr. Lin did not "choose" to develop the EPV and EPQ probes from the amino acid sequence information of fragments 35 and 38. He used fragments 35 and 38 to design his probes because they were among the first fragments to be sequenced. (Lin, Tr. 360-363)

366. Following Dr. Lin's design and order, the EPV and EPQ probes were constructed either manually or by machine. Dr. Lin did not develop the techniques for making such probes. (Lin, Tr. 311-313)

367. Both the mechanical and manual techniques for the synthesis of oligonucleotide probes were available prior to 1983. (Lin, Tr. 313)

368. The technique of using oligonucleotide probes was in its early stages in 1981. At least one publication proposed the use of mixed oligonucleotide probes for finding genes in a DNA library; however, the publication only suggested the screening of cDNA libraries, not gDNA libraries, which are far larger and more complex. (Lin, Tr. 283-284)

369. Dr. Lin's research began with a genomic DNA library obtained from Dr. Maniatis. The library was commercially available to many researchers. (Lin, Tr. 314)

370. The library comprised 1,500,000 phage plaques in lambda phage. (CX-91 at 3)

371. After obtaining the library from Dr. Maniatis, Dr. Lin employed a procedure for lysing the phage and fixing it to the filters. This procedure by itself was not developed by Dr. Lin. (Lin, Tr. 315)

372. The EPV and EPQ probes comprise two pools of oligonucleotide probes. Each pool comprised 128 oligonucleotide probes. The EPQ probes were 17 nucleotides in length, and the EPV probes were 20 nucleotides in length. (Lin, Tr. 321; CX-91C; CX-60; CX-129C)

373. Each one of these oligonucleotide probes is radioactively labeled. When concentrated into a pool with 128 probes, the amount of radioactivity was substantial[illegible]ncreased. The high radioactivity not only imposed a health risk to pers[illegible] working with these probes, but also

created a great deal of radiation background noise that interfered with attempts to tag the EPO gene using these radioactive probes. (Lin, Tr. 319-321)

374. In oligonucleotide screening, there are many signals in the background and the filter itself can create signals during the screening process. Therefore, in order to eliminate false signals, Dr. Lin chose to match signals from two sets of probes. Where the signals from the two sets of probes match closely, Dr. Lin treated the match as a potential candidate. (Lin, Tr. 366)

375. After the procedure of matching two signals, the region where the matches occurred are typically rescreened with probes. During the rescreening process the phage are placed on the filters at a lower density so there is less interference from the membrane phage. Because rescreening is done at a lower density, the problem with the background is also reduced. (Lin, Tr. 366)

376. Although other researchers had previously used mixed pools of radioactively labeled oligonucleotide probes, Dr. Lin was the first researcher to use such probes to screen the human genomic library. Prior utilization of radioactively labeled oligonucleotide probes had been limited to screening cDNA libraries. (Lin, Tr. 321-322)

377. To screen one and a half million phages, Dr. Lin used 30 filters with approximately 50,000 plaques per filter. The 30 filters each containing 50,000 phages were then screened with the mixed oligo probes. (Lin, Tr. 358)

378. The mixed oligo probes used by Dr. Lin were based on fragment 35 and fragment 38, which were among the tryptic amino fragments supplied by

Dr. Goldwasser. Each fragment contained the amino acid tryptophan. (Lin, Tr. 358-359)

379. Although the amino acid sequence information in fragment 35 was less degenerate than amino acid sequences that Dr. Lin had previously employed, the amino acid sequence in the fragment was still highly degenerate, i.e., a degeneracy of 128, because it contained all of the codons encoded by six or seven amino acids. (Lin, Tr. 359)

380. The EPV probes used by Dr. Lin were 20 nucleotides (or "mers") long. The length of mer of a probe is measured by the number of nucleotides in the probe. If a shorter probe of 17 mer had been chosen by Dr. Lin, the degeneracy could have been less. However, Dr. Lin selected a 20 mer probe because a shorter probe reduces the specificity of its hybridization. (Lin, Tr. 360)

381. Dr. Lin first screened the 1,500,000 phage human genomic library, i.e., 30 filters with 50,000 phages on each filter, with the EPV probe mixture. This resulted in 270 strong signals. (Lin, Tr. 364-365)

382. The EPV probes were washed off after the initial screening. The filter was then rescreened by the 128 oligonucleotide probes from the next EPQ probe mixture. (Lin, Tr. 367)

383. Where the signals from the first screening and the second screening correspond, a potentially correct clone is within the group which hybridizes to both mixtures. (Lin, Tr. 367)

384. Dr. Lin identified 43 potentially correct clones from the 1,500,000 phage library by screening and matching the two 128 probe mixtures. The 43 potentially correct clones were then replated on different filters. (Lin, Tr. 368)

385. After more than two years of effort, the approach which finally succeeded in isolating and cloning the EPO gene utilized the two sets of 128 nucleotide probes to screen a genomic DNA library containing 1.5 million phage particles. (Lin, Tr. 242)

386. After screening the library with these probes, Dr. Lin was able to narrow the library from 1.5 million phage particles down to approximately 40 potentially positive signals. At this point, Dr. Lin recognized that he had made a potentially significant development in his research. (Lin, Tr. 242-243)

387. After the potential clones are replated they are screened repeatedly with up to 5 runs of rescreening and two sets of probes are used to make sure that each spark picked up by the first set of probes is a real one. (Lin, Tr. 372)

388. With respect to the example set forth at column 21 of the '008 patent which reports three clones, Dr. Lin rescreened some potential clones with less than 128 probes and some with the full amount. (Lin, Tr. 373)

389. Some of the potential positive clones were rescreened with probes from subsets 1, 2 and 5 of the EPV mixture and those subsets had 48 probes, but others were rescreened with EPV 1-8 and EPQ 1 where each set was 128 probes. (Lin, Tr. 374)

390. In Dr. Lin's opinion the best way to screen the EPO gene was to use the full mixtures of 128 probes. (Lin, Tr. 370)

391. No researchers prior to Dr. Lin were reported to have utilized two sets of 128 nucleotide probes to screen a genomic library. (Lin, Tr. 242)

392. Although it is possible to screen for the EPO gene without the full mixture of probes, complications may arise because the clone that was first screened out may not be visible. (Lin, Tr. 370)

393. The screening ultimately identified four potentially positive clones. These clones were subjected to nucleotide sequence analysis in order to deduce the primary structural conformation of the erythropoietin polypeptides encoded thereby. Three of the four clones which had hybridized with both probe mixtures were confirmed as erythropoietin clones, as confirmed by subsequent analysis. (CX-91 at 3)

394. After Dr. Lin cloned the EPO gene, he began receiving substantial assistance from other scientists at Amgen to help sequence and express the gene and assay the protein. Dr. Lin was recognized by his fellow employees at that time as the person responsible for success in the EPO project. (Lin, Tr. 244-247)

395. After cloning the erythropoietin gene the strategy at Amgen was to transfect a host cell with the EPO DNA sequence. (Lin, Tr. 375-376)

396. In order to confirm that the phage particles or clones identified as potentially positive signals by the two sets of probes actually contained the EPO gene, Dr. Lin's team had to isolate, purify, and sequence the genes, and express the gene so as to yield the protein product. The biological activity of the product expressed by these genes was examined, and it proved to be EPO, meaning that it increased red blood cell production. This proved that the gene isolated by Dr. Lin was in fact the EPO gene. (Lin, Tr. 245-246)

397. It was known before the EPO gene was cloned that EPO was a glycosylated protein. It was also known that mammalian cells have the

capacity to glycosylate proteins. However, it was not known whether a mammalian cell would be able to glycosylate erythropoietin to a biologically active state. (Lin, Tr. 376)

398. In order to create host cells capable of producing recombinant erythropoietin, the DNA sequence encoding erythropoietin was replicated. The resultant recombinant vector containing the erythropoietin sequence was then transfected into a mammalian host cell in a manner allowing the host cell to express erythropoietin. The transfected host cell is capable of glycosylating and secreting the erythropoietin protein produced within the host cell to produce active recombinant human erythropoietin as a glycoprotein polypeptide. (CX-91C at 2)

399. The transfected mammalian host cells expressed glycosylated erythropoietin which was isolated, purified, and tested to confirm its biological activity in the production of red blood cells, thus confirming that Dr. Lin had successfully isolated and identified the DNA sequences encoding human erythropoietin. (CX-91 at 4)

400. There appear to be no differences in the secondary structure of EPO produced in a CHO cell versus EPO produced in a human kidney cell. (Goldwasser, Tr. 82).

401. Tertiary structure of either recombinantly produced EPO or naturally occurring EPO is unknown at the present time. (Goldwasser, Tr. 82).

402. Based on extensive testing and carbohydrate analysis, the researchers at Genetics Institute were unable to find any significant differences between the carbohydrate structure of urinary erythropoietin versus recombinant erythropoietin. (Shoemaker 1021-1023).

403. In terms of biological function, i.e. having the same effect on causing red cells to be produced in the body, recombinant EPO and natural EPO are the same. (Lin, Tr. 424).

404. Dr. Lin could not recite any specific qualitative differences in the translation process between the host cell and the human kidney cell. (Lin, Tr. 422).

405. This work by Dr. Lin resulted in the filing of a U.S. patent application on December 13, 1983, which eventually provided the basis for the issuance of U.S. Patent No. 4,703,008. (CX-91 at 4)

406. Dr. Lin does not lay claim to being the inventor of the general concept of putting exogenous DNA in an expression vector, or the concept of using that vector to transform or transfect a host cell. (Lin, Tr. 275-276)

407. Dr. Lin states that the generalized transcription, translation, glycosylation, and secretion processes apply to all cells. However, in the recombinant host cells the actual processes going on inside the cells are different from those in natural cells which make EPO. (Lin Tr. 261-262)

408. The host cell intracellular processes, however, cannot be described on the basis of current knowledge. (Lin, Tr. 275)

409. Dr. Lin considers that he was the first to discover the EPO gene. (Lin, Tr. 274)

410. Dr. Shoemaker recognizes that Amgen was the first to discover the EPO gene. (Shoemaker, Tr. 1037)

2. Scope And Content Of Prior Art

411. The field of the invention or relevant art concerns the cloning

of genes and expression of recombinant products, particularly EPO. (Sadler Tr. 850; Ullrich Tr. 667)

412. In 1982-1983, various genes had been cloned, however, they were either over expressed in some organ or cell type or represented a major portion of a certain tissue source. (Ullrich, Tr. 666)

413. In 1982-1983, there was no knowledge available about the EPO gene and only minimal knowledge about the amino acid sequence of EPO itself. (Ullrich, Tr. 666)

414. The prior art is represented by more than 160 references cited by Dr. Sadler, the expert of Chugai. (Sadler, Tr. 860)

415. In the time period prior to September 1983, there were several publications available which generally described the methodologies with respect to the use of oligonucleotides for screening libraries. (Sadler, Tr. 828-829).

416. Respondents' Exhibit 74, an article by Wallace et al. lays the ground work for the use of mixed oligonucleotides as probes by determining the effect of mismatches between probe sequences and target DNA sequences on the stability of the hybrid molecule formed when it is used as a probe. The article showed that it was possible to distinguish a perfect match from a hybrid containing only a single mismatch. (Sadler, Tr. 831).

417. Respondents' Exhibit 75 also by Wallace et al., first describes the use of synthetic oligonucleotides as hybridization probes, using a mixture of relatively short oligonucleotides derived from the sequence of a rabbit hemoglobin protein to screen purified CDNA for rabbit betaglobin. (Sadler, Tr. 831).

418. Respondents' Exhibit 70, by Suggs et al., describes the use of mixed oligonucleotide probes to clone a CDNA for a human protein called beta-two microglobin. This article shows the utility of the approach for cloning previously uncloned human CDNA's. (Sadler, Tr. 832).

419. Respondents' Exhibit 78, by Whitehead et al., used mixed degenerate oligonucleotide probes to isolate a CDNA clone of another human protein called, compliment component C4. In this paper a probe mixture containing 384 different sequences, comprising all possible 23 nucleotide long sequences that could encode a certain segment of this protein, was used to successfully screen a human liver CDNA library to isolate a clone for human compliment component C4. (Sadler, Tr. 832-833) (Ullrich, Tr. 726). ('008 patent, Col. 39, lines 45-55).

420. Respondents' Exhibit 96 is a paper by Jaye et al., in which the author describes the use of a long probe of unique sequence to successfully clone human factor 9. In this strategy protein sequence derived from the bovine or cow-protein was used to devise a long oligonucleotide probe, using guesses in the positions of potential degeneracy. A probe of 52 nucleotides in length was synthesized and used to screen a human liver CDNA library in a clone for human factor 9. (Sadler, Tr. 833-834).

421. Respondents' Exhibit 79 by Anderson and Kingston, describes the use of a different long oligonucleotide to screen a genomic DNA library from a cow and successfully isolate a clone for a protein known as pancreatic trypsin inhibiter. (Sadler, Tr. 834).

422. Respondents' Exhibits 70, 78, 79, 96, 99 and 100 are published articles representative of the type of techniques that were being used in the art in the time frame of 1982 and 1983, involving the use of mixed

oligonucleotide probes. These articles show the use of mixed oligonucleotide probes in the screening of DNA clone libraries. (Shoemaker, Tr. 946-947).

423. The articles which Dr. Sadler reviewed and the seven to which he testified relate to the field of genetic engineering but do not refer specifically to erythropoietin. None describes or reports the cloning of EPO. (Sadler, Tr. 860 and 842-844)

424. The following genetic engineering tools and techniques were also known and available to Biogen in attempting to clone the erythropoietin gene; human genomic library, gene screen plus filters, NZYAM plates, digestion with proteinase, prehybridization with SDS buffer, hybridization temperature calculations, mixed probes, technique of insertion of a DNA sequence into a vector or sequence, transfection of a mammalian host cell with a DNA sequence, manual and automatic sequencing of amino acids of proteins and their fragments, a trypsin digest of a protein to divide it into more handleable fragments for sequencing. (Davies, Tr. 453-455)

425. In 1983 the technology for making the probes had advanced to a point where the probes could be synthesized automatically by machine. (Davies, Tr. 464-465)

426. People of ordinary skill in the art in 1983 used the approach of screening both cDNA and gDNA libraries although it was predominantly cDNA libraries up until 1983. (Davies, Tr. 477)

427. The knowledge of the correct amino acid of the protein does not insure the selection of the correct probes for isolating the gene. (Davies, Tr. 462)

428. The technology for transforming or transfecting mammalian host cells with exogenous DNA was available to scientists in 1983 and Amgen scientists as well as other scientists. Had the code for EPO been available, a scientist would have been able to insert the human genomic clone for erythropoietin into a plasmid and transform or transfect it into a COS cell or CHO cell. (Lin, Tr. 377-378)

429. The filters and mediums and prehybridization techniques that Dr. Lin used were also available prior to Dr. Lin's work. (Lin, Tr. 318-319)

430. It was known in 1983 and prior how to make mixed oligonucleotide probes. (Davies, Tr. 464-465)

431. With regard to using probes to screen the erythropoietin gene success is never assured regardless of the approach. (Sadler, Tr. 854)

432. Many factors can conspire to make the project unsuccessful. (Sadler, Tr. 854)

433. Dr. Sadler provides in his witness statement the following references as being pertinent to the use of oligonucleotide probes in screening a library. (Sadler Tr. 828-834)

> Whitehead et al., Use of a cDNA clone for the forth component of human complement (C4) for analysis of a genetic deficiency of C4 in guinea pig, Proc. Nat'l. Acad. Sci. USA, Vol. 80, pp. 5387-5391, September 1983. (RX-78)
>
> Breslow et al., Isolation and characterization of cDNA clones for human erythropoietin A-I, Proc. Nat'l. Acad. Sci. USA, Vol. 79, pp. 6891-6865, November 1982. (RX-99)
>
> Woods et al., Isolation of cDNA clones for the human complement protein factor B, a class III major histocompatibility complex gene product, Proc., Natl. Acad. Sci. USA, Vol. 79, pp. 5661-5665, September 1982. (RX-100)

Wallace et al., The use of synthetic oligonucleotides as hybridization probes. II Hybridization of oligonucleotides of mixed sequence to rabbit B-globin DNA, Nucleic Acids Research, Vol. 9, No. 4, pp. 879-894, 1981. (RX-75)

Wallace et al., Hybridization of synthetic oligodeoxyribonucleotides phage lambda 174 DNA: The effect of single base pair mismatch, Nucleic Acids Research, Vol. 6, No. 11, 1979. (RX-74)

Suggs et al., Use of synthetic oligonucleotides as hybridization probes: isolation of cloned cDNA sequences for human B_2 - microglobin. Proc. Nat'l Acad. Sci., Vol. 78, No. 11, pp. 6613-6617, November 1981. (RX-70)

434. Dr. Shoemaker chose six prior art references as illustrative of the state of the art in regards to the use of mixed oligonucleotide probes to screen for desired clones. These references were:

(1) Kornblihtt et al., Isolation and characterization of cDNA clones for human and bovine fibronectins, Proc. Natl. Acad. Sci. USA, vol. 80, pp. 3218-3222, June 1983. (RX-79)
(2) Jaye et al., Isolation of a human anti-hemophilic factor IX cDNA clone using a unique 52-base synthetic nucleotide probe deduced from the amino acid sequence of bovine factor IX, Nucleic Acids Research, vol. 11, no. 8, pp. 2325-2335, 1983. (RX-96)
(3) Suggs et al., Use of synthetic oligonucleotides as hybridization probes: Isolation of cloned cDNA sequences for human B_2-microglobin, Proc. Natl. Acad. Sci. USA, vol. 78, no. 11, pp. 6613-6617. (RX-70)
(4) Woods et al., Isolation of cDNA clones for the human complement protein factor B, a class III major histocompatibility complex gene product, Pro. Natl. Acad. Sci. USA, vol. 79, pp. 5661-5665. September 1982. (RX-100)
(5) Breslow et al., Isolation and characterization of cDNA clones for human apoliproprotein A-I, Proc. Natl. Acad. Sci. USA, pp. 6861-6865, November 1982. (RX-99)
(6) Whitehead et al., Use of a cDNA clone for the fourth Component of human complement (C4) for analysis of a genetic deficiency of C4 in guinea pig, Proc. Natl. Acad. Sci. USA, pp. 5387-5391, September 1983. (RX-78)

(Shoemaker, Tr. 996)

435. Dr. Shoemaker cites the following references as significant findings regarding glycosylation of proteins produced by recombinant methods as of 1983:

(1) Hayes and Weissman, "Production of a Glycosylated Human Protein by Recombinant DNA Technology", Humoral Factors Host Def. Proc. Sci. Found. Symp. Biosci. (1983) 1st, Meeting Date 1982, 111-29. (RX-41)
(2) Moriartz A.M. et al., "Expression of the Hepatitis B. Virus Surface Antigen Gene in Cell Culture by Using a Simian Virus 40 Vector", Proc. Natl. Acad. Sci. USA 78, 2606-10 (1981). (RX-65) (Shoemaker, Tr. 947-949)

3. Differences between the Prior Art and the Claims at Issue

436. All of the prior art references relied upon by Dr. Shoemaker dealt with screening a cDNA library, not a genomic library which was used by Dr. Lin. (Shoemaker, Tr. 993)

437. Genomic DNA libraries are approximately 100 times more complicated than cDNA libraries. (Lin. Tr. 285-289)

438. For example, the largest cDNA library size involved in the six prior art references selected by Dr. Shoemaker was 50,000 plaques (present in the Woods and the Whitehead references). The Suggs et al. prior art reference had a library of 535 plaques. (Shoemaker, Tr. 980-996; CPX-40)

439. Dr. Lin, by way of contrast, worked with a gDNA library that contained 1.5 million plaques. (CX-1; CX-91 at 3 and Lin, Tr. 358)

440. The desired clones of the six prior art references selected by Dr. Shoemaker were present in the libraries of those references at levels ranging from a high of 1:500 (in Breslow) to a low of 1:3100 (in Whitehead). (Shoemaker, Tr. 980-996; CPX-40)

441. Dr. Lin cloned the EPO gene notwithstanding that it was present only in 3 positives clones in the 1.5 million library, i.e. a ratio of 1:500,000. (Lin 371-372; CX-1)

442. Moreover, none of the prior art references selected by Dr. Shoemaker purport to disclose cloning of the human EPO gene. (RX-79; RX-96; RX-70; RX-100; RX-99; and RX-78)

443. The expression of erythropoietin in the Chinese ovary cell is unregulated. It is tonically on. That is desirable from the standpoint of producing a protein in large quantities. It is clearly not regulated in the same way that the erythropoietin gene is regulated in its natural cell. (Sadler, Tr. 858)

444. By tonically on, Dr. Sadler means that the gene is always being transcribed at a comparatively high rate, i.e., that it is consecutively or permanently expressing erythropoietin. (Sadler, Tr. 858-589)

445. By contrast the cell, presumably in the kidney, that makes erythropoietin is sometimes on and sometimes less on. (Sadler, Tr. 858-859)

446. Dr. Shoemaker, Chugai's expert who worked at G.I. from 1981 until 1987, stated that it was an important scientific discovery to have ascertained the sequence for EPO. (Shoemaker, Tr. 977; RX-2)

447. Dr. Fritsch of G.I. believed that the identification of the genomic clone for EPO was a significant discovery. (CPX-34-3C (Fritsch Dep.), at 151)

448. On January 3, 1985, G.I. filed its own patent application containing claims directed to a host cell for the production of recombinant erythropoietin. (Shoemaker, Tr. 974; CX-82)

4. Level of Ordinary Skill in the Art

449. Persons of ordinary skill in the field of the invention or

relevant art are molecular biologists and/or persons skilled in recombinant DNA technology. (Ullrich Tr. 663-664; Sadler Tr. 843)

450. The level of skill in the art of cloning in 1982-1983 was high. It was typically a person having Ph.D. in the field with one or two years post doctoral experience. (Ullrich, Tr. 665)

451. The other scientists that Dr. Lin worked with at Amgen in the genetic engineering field for the most part had advanced degrees, i.e., Ph. D.'s. (Lin, Tr. 279-280).

5. Failure of Others

452. Another company engaging in efforts to make recombinant EPO was Biogen. Biogen, a company engaged in biotechnology research and product development, was started in 1978. The sole objective of Biogen in the early days was to isolate genes of rare proteins, to clone those genes into appropriate organisms, and to produce the product with the intention of developing products for pharmaceutical use. (Davies. Tr. 444-445)

453. In 1981, after cloning and expressing Alpha Interferon and Beta Interferon, Biogen began work on trying to clone the gene for EPO in an appropriate producing organism. It began work on EPO after discussions with medical experts, and in particular a number of hematologists recommended EPO as a good subject for research. Dr. Julien Davies was responsible for overall supervision of the Biogen EPO project. (Davies, Tr. 446-447)

454. Dr. Davies was the first Research Director of the Biogen laboratory in Geneva, Switzerland. While there, he engaged in the development of human proteins for therapeutic and pharmaceutical use. (Davies, Tr. 445)

455. Dr. Davies is a Ph.D. biotechnologist employed in the biotechnology department at the Institut Pasteur in Paris, France. He has taught molecular biology, biochemistry, biotechnology and genetics at Columbia University, University of Wisconsin, Institute Pasteur and at Harvard Medical School. Dr. Davies has received a Distinguished Teaching Award at University of Wisconsin and the Hoechst-Roussel Award of the American Society of Microbiology, and also an Honorary Degree at the University of Zaragoza in Spain. He has published about 170 papers describing his research work. Dr. Davies is an expert in Biotechnology. (Davies, Tr. 440-444; CX-5)

456. The persons at Biogen involved in the attempt to clone the EPO gene included Dr. Walter Gilbert of Harvard University who is a Nobel Prize winner, Prof. Bernard Mach who is extremely well known for his work on HLA locus and for heading one of the first laboratories to carry out cDNA cloning, and Dr. Richard Flavell, a fellow of the Royal Society in London, who became the Director of the Biogen lab in Cambridge and was also involved in the direction of this project. These individuals, as well as other Biogen employees were chosen for their expertise either in the areas of gene cloning, gene expression, or protein isolation. Additionally, Biogen had a number of consultants including Ishmael Zanjani, a hematologist at the University of Minnesota who had worked a great deal with EPO. (Davies, Tr. 447-449)

457. Biogen's level of financial commitment to its EPO project from the end of 1981-1984 was approximately 6 million dollars. (Davies, Tr. 450 and 489)

458. Several approaches in research were taken by the Biogen teams which attempted to clone the EPO gene. One approach was the isolation of messenger RNA. Another was the use of synthetic DNA probes in a cDNA library, and a third approach was trying to obtain antibodies in order to detect messenger RNA. These approaches were taken because Biogen had had success in cloning other genes with them. Greater emphasis was given to the messenger RNA routes by Biogen because of their prior research expertise in that area. (Davies, Tr. 451-453)

459. Biogen had a lot of information about the amino acid sequence of EPO, but it was usually wrong. The first knowledge of any sequence information of the amino acid sequence that Biogen had was from Lee Hood's laboratory in California. Biogen obtained some partial N-terminal sequence of the amino acid. (Davies, Tr. 479-480).

460. Biogen used the sequence information from Lee Hood's laboratory to synthesize peptides and to make oligonucleotide probes but the sequence turned out to be wrong or had mistakes and the mistakes meant that the antibody was not suitable and that the probes were not suitable probes. (Davies, Tr. 480).

461. Biogen tried but failed to successfully screen the human genomic library for erythropoietin. Biogen purified the EPO they received from Green Cross Corporation, did tryptic digestion, sequenced some of the tryptic fragments and made mixed oligonucleotide probes. Biogen used these probes to screen all of their C-DNA libraries, but found no positives that screened through to the end. (Davies, Tr. 493-494)

462. The problem that Biogen had was that the protein that they were

using upon which they based the probes turned out not to be EPO. (Davies, Tr. 486-487).

463. When Biogen heard that Amgen had used a human genomic library they used the probes derived from the EPO which they had received from Green Cross to screen a human genomic library. They did not find the EPO gene. (Davies, Tr. 494)

464. Biogen did not try a different region, having been unsuccessful with the region they were working with because they didn't have the probes that long before the GI paper came out. They only worked on that particular screening effort a couple of months before the Genetics Institute paper came out disclosing the DNA sequence for EPO. By then it was known that Amgen had cloned the human EPO gene so Biogen decided to give up the project. (Davies, Tr. 450, 497).

465. Dr. Davies believes that if Biogen had had the amino acid sequence information of the tryptic fragments of EPO that are reported in the '008 Amgen patent, it should have cloned the EPO gene in 1983. (Davies, Tr. 503).

466. If Biogen had a library with a gene or part of a gene the same as Genetics Institute had, they also believe they would have, in principle, isolated the EPO gene. (Davies, Tr. 504).

467. Since its attempts to first clone the EPO gene were a failure, Biogen did not publish its results. (Davies, Tr. 494)

468. Biogen's erythropoietin project was terminated at a scientific board meeting towards the end of 1984. (Davies, Tr. 498)

469. Although Biogen was not successful in first cloning the EPO gene, it was successful in cloning a number of other genes. Biogen was

successful in cloning the reductase gene. The reductase gene was cloned using mixed oligonucleotide probes. Biogen was also successful in cloning the Factor VIII gene using mixed oligonucleotide probes. Biogen was successful in its efforts to clone Interleukin II and CSF (colony stimulating factor). (Davies, Tr. 468-472)

470. During the period that Biogen was attempting to clone the EPO gene, Dr. Davies heard that not only Amgen but Genetics Institute, Integrated Genetics and a Japanese company were reportedly interested in cloning EPO. (Davies, Tr. 492)

471. Biogen heard that Amgen had succeeded in cloning the EPO gene. The first information that let Biogen know how it was done came "through the grapevine" and was that Amgen had successfully cloned EPO by screening a human genomic library. (Davies, Tr. 492-493)

472. Another genetic engineering company which attempted to clone the EPO gene was Genentech. Dr. Axel Ullrich and the personnel in his laboratory at Genentech failed to clone EPO before Amgen. (Ullrich, Tr. 659)

473. Dr. Ullrich obtained a Ph.D. in Biochemistry and Molecular Genetics in 1975 from the University of Heidelberg, West Germany. In October of 1975, Dr. Ullrich undertook research in the Department of Biochemistry and Biophysics at the University of California, San Francisco. Since 1979, Dr. Ullrich has been a scientist at Genentech in South San Francisco. Dr. Ullrich has received a number of awards both in this country and abroad for his accomplishments in the area of recombinant DNA technology and molecular biology. Dr. Ullrich is presently a member of the Editorial Board or a reviewer for a large number of scientific journals.

Over the last twelve years, Dr. Ullrich has published over 100 articles, book chapters on the molecular biology of human disease and the function of hormones and receptor molecules and the control of cellular functions, growth and differentiation. Dr. Ullrich's Ph.D. thesis dealt with the mechanisms by which messenger RNA is translated in various types of systems, including viral systems. (Ullrich, Tr. 651-654)

474. Dr. Ullrich is an expert in molecular biology and recombinant DNA technology. (Ullrich, Tr. 663-664; CX-92C)

475. In 1981, Dr. Ullrich decided to attempt to clone the gene for EPO. (Ullrich, Tr. 661)

476. Prior thereto, in 1975, Dr. Ullrich was the first researcher to successfully clone a recombinant DNA product, insulin. Dr. Ullrich continued the insulin project after joining Genentech in 1979, and eventually succeeded in producing a pharmaceutical product composed of recombinant human insulin. (Ullrich, Tr. 657)

477. Subsequent to his work on human insulin, Dr. Ullrich began researching insulin-like growth factors. In the last ten to twelve years, Dr. Ullrich's laboratory has cloned more than 20 genes, many of which Dr. Ullrich cloned himself. (Ullrich, Tr. 658)

478. Dr. Sadler is familiar with Dr. Axel Ullrich's gene cloning work and considers him to be "... a very expert cloner." (Sadler, Tr. 854)

479. In his various cloning activities, Dr. Ullrich has employed virtually all the technologies available, including cDNA cloning, genomic cloning, and chemical synthesis of genes. Dr. Ullrich has screened cDNA libraries and extensively utilized oligonucleotide probes. (Ullrich, Tr. 658-659)

480. It was known that a decrease in oxygen in the circulation, whether caused by an actual decrease in the amount of oxygen in the atmosphere or by a decrease in the amount of red blood cells in the circulation, will stimulate the production of erythropoietin. Because of this characteristic, Dr. Ullrich decided to follow two courses in his attempt to obtain mammalian EPO from which he could determine the amino acid sequence. First, anemic conditions were induced in rabbits through the injection of phenylhydrazine, which destroys red blood cells. Second, hypoxic conditions were induced in mice. The kidneys of these animals were then isolated in an attempt to identify, through differential screening methods, the genes representing EPO. (Ullrich, Tr. 662-663)

481. The preparations for this project took more than one year. Prior to the conclusion of the project, Dr. Ullrich heard rumors that Amgen had already succeeded or was close to succeeding in cloning the EPO gene, and therefore decided to abandon the project. (Ullrich, Tr. 662-663)

482. Dr. Fritsch of G.I. also undertook to clone EPO. (CPX-34-3C (Fritsch Dep.), at 7)

483. Dr. Fritsch came to work at G.I. in April of 1982 (CPX-34-3C (Fritsch Dep.), at 7)

484. The focus of Dr. Fritsch's work at G.I. was molecular cloning of erythropoietin. (CPX-34-3C (Fritsch Dep.), at 7)

485.

486. Dr. Fritsch successfully cloned a cDNA library for erythropoietin sometime after June of 1984. (CPX-34-3C (Fritsch Dep.), at 14)

487. The significance of the Amgen invention is that it allows, for the first time, the expression of EPO in quantities sufficient to undertake research regarding the hormone and clinical treatment of patients suffering from anemia. (Lin, Tr. 251)

488. Dr. Shoemaker, Chugai's expert who worked at G.I. from 1981 until 1987, stated that it was an important scientific discovery to have ascertained the sequence for EPO. (Shoemaker, Tr. 977; RX-2)

489. Dr. Fritsch of G.I. believed that the identification of the genomic clone for EPO was a significant scientific discovery. (CPX-34-3C (Fritsch Dep.), at 151)

B. Inequitable Conduct

490. Although the prior art Sue et. al. reference taught part of the amino acid sequence for EPO, the Sue et. al. reference contained errors in the reported amino acid sequence. (RX-21C (Borun Dep.), at 288 and 291-292)

491. Chugai's own technical expert, Dr. Shoemaker, acknowledged that Genetics Institute and others tried but failed to isolate the human EPO gene using such partially incorrect amino acid sequence information. (Shoemaker, Tr. 887-889 and 889-890)

492. The prosecution history shows that the Sue et. al. reference was distinguished on several different grounds, i.e., (1) Amgen did not do what the Examiner said could have been done using the Sue et. al. reference, (2) some prior art references, e.g., Anderson et. al. (reference "C2" of the prosecution history) argued that the method suggested by the Examiner was impractical; (3) the practical consequence of the errors in the Sue et. al. reference was that probe sequences which included the erroneous information

could not have been employed to detect the EPO gene; (4) probe sequences which avoided the erroneous information would have been either too degenerate or too short to use in isolating the EPO gene; and (5) the screening approach which succeeded in cloning the EPO gene was more complex than the approaches in any of the prior art cited by the Patent Examiner. (CX-2 at 355-365)

C. Dr. Lin Is The Sole Inventor

493. Dr. Lai, like Dr. Lin, was an employee of Amgen at all times pertinent to his involvement in the EPO project, i.e., from October, 1982 until September, 1987. (RX-18C (Por Lai Dep.), at 13-15)

494. The EPO project at Amgen was already underway prior to the time that Dr. Lai joined Amgen. (RX-18C (Por Lai Dep.), at 17-18)

495. Dr. Lai's involvement in the EPO project was in the protein chemistry area, as opposed to the DNA area. (RX-18C (Por Lai Dep.), at 17)

496. As previously noted, it was Dr. Lin -- not Dr. Lai -- who designed and ordered the DNA probes which successfully isolated the human EPO gene. (Lin, Tr. 313-315; CX-60; CX-129C)

497. Prior to his deposition in this matter, Dr. Lai had not seen the documents by which Dr. Lin designed and ordered the DNA probes which successfully isolated the human EPO gene. (RX-18C, (Por Lai Dep.), at 69 and 84; CX-60; CX-129)

498. After he sequenced the amino acid fragments prepared by Dr. Goldwasser and delivered his sequencing results to Dr. Lin, Dr. Lai had no further activity in the successful isolation and cloning of the human EPO gene. (RX-18C (Por Lai Dep.), at 87)

499. Dr. Lai admitted that he is not familiar with the detailed procedure used by Dr. Lin for cloning the human EPO gene. The mixed probe procedures used by Dr. Lin to screen DNA libraries is described in some detail in the patent. (RX-18C (Por Lai Dep.), at 89-90)

500. Dr. Lai admitted that he has never personally performed the laboratory work needed to screen for genes or hybridize probes with the EPO gene. (RX-18C (Por Lai Dep.), at 113-134)

501. There were many instances where amino acid sequence information was available to the art, yet having that information available did not, per se, constitute the isolation and cloning of the desired gene. For example, Dr. Davies explained that Biogen had internal amino acid sequence information for the EPO gene, yet was unable to isolate the gene. (Davies, Tr. 463) Dr. Ullrich related other instances where amino acid sequence information for a protein was known, yet the gene responsible for the protein was not isolated and cloned despite the effort of many good molecular biology laboratories. (Ullrich, Tr. 660-661)

VIII. CHUGAI'S MANUFACTURING PROCESS, IF PRACTICED IN THE UNITED STATES, WOULD INFRINGE THE AMGEN '008 PATENT

A. The Chugai Process In General

502. Chugai's first efforts toward becoming a manufacturer of recombinant erythropoietin took place in the middle of 1984 when Chugai entered into a contract with Genetics Institute. (CPX-7 (Kawaguchi Dep.), at 32; CX-10)

503. EPOCH is the name for the development of EPO by Chugai. (CPX-5C (Nogaki Dep.), at 10)

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506. The production technology research labs of Chugai, which are under the production division, have responsibility for the manufacture of recombinant EPO by Chugai. (CPX-7 (Kawaguchi Dep.), at 38)

507. The production technology research lab is located in Ukima, Kita ku, Tokyo. (CPX-7 (Kawaguchi Dep.), at 39)

508. There are no Chugai departments or sections involved in the production of recombinant EPO other than the production technology research lab at Ukima. (CPX-7 (Kawaguchi Dep.) at 39-40)

509. Chugai ultimately completed the construction of a production facility for the manufacture of human erythropoietin in February of 1986. (CPX-5C (Nogaki Dep.), at 26)

510. The facility used for the manufacture of human EPO by Chugai is located in Ukima, Japan. (CPX-5C (Nogaki Dep.), at 34)

511. From April of 1986 to the present, the Chugai production facility has been used for the manufacture of human EPO. (CPX-5C (Nogaki Dep.), at 26)

512. G.I. has been the sole source of all of the host cells used by Chugai in the manufacture of human EPO in Japan. (CPX-5C (Nogaki Dep.), at 36)

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562. Chugai uses a eucaryotic host cell in manufacturing recombinant EPO in Japan. The host cell utilized by Chugai in the manufacture of recombinant EPO in Japan has been transformed or transfected with a vector containing a DNA sequence coding for EPO. (Counsel, Tr. 592; CX-181)

563. Within the host cell utilized by Chugai in the manufacture of recombinant EPO in Japan, A DNA sequence is transcribed into mRNA, and mRNA is translated into EPO. (Counsel, Tr. 593; CX-181)

564. The host cell utilized by Chugai in Japan to manufacture recombinant EPO glycosylates the EPO. (Counsel, Tr. 593; CX-181)

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B. The Chugai Process

569. Dr. Thomas Randolph Wall studied the Chugai process for the manufacture of recombinant erythropoietin by review of the '008 patent, the prosecution history for the '008 patent, the prior art cited by Chugai, the

interrogatories of Chugai, the answers by Chugai to requests for admission; the stipulation between the parties, the Kawaguchi deposition, and the Nogaki deposition. (Wall, Tr. 589-592)

570. Dr. Wall is a professor in the Department of Microbiology and Immunology in the School of Medicine at UCLA. His primary duties are in the area of research, although he also teaches medical students and graduate students. Dr. Wall received a Ph.D. in Microbiology from Indiana University in 1970. After receiving his degree, Dr. Wall undertook studies of the regulation of gene expression in eucaryotic cells at Columbia University, and has continued those studies since joining the faculty of UCLA. Dr. Wall has published approximately 60 articles on the molecular biology of eucaryotic gene expression, and control, as well as on the human immune response. Dr. Wall was a founder and is a member of the Board of Directors of Ingene, Inc., a genetic engineering company located in Santa Monica, California. Dr. Wall is also a member of the Scientific Advisory Board of FMC Corporation, and has served on the Editorial Board of the Journal of Immunology and the Journal of Molecular and Cellular Immunology. Dr. Wall is presently on the National Education Committee of the American Association of Immunologists. Dr. Wall's research in the area of gene expression has focused on the process by which genes are transcribed into mRNA, including the regulation of that process and its relationship to the immune response. Dr. Wall is an expert in the fields of molecular biology and gene expression. (Wall, Tr. 585-588; CX-6)

571. Dr. Wall testified regarding the application of certain claims of the Lin '008 patent to the Chugai process. (Wall, Tr. 585-640)

572. The process utilized by Chugai in Japan to make recombinant EPO uses a sequence as described by claim 7 of the '008 patent. (Wall, Tr. 605)

573. Each and every descriptive term utilized in claim 7 of the '008 patent describes an aspect of the Chugai process. Chugai's process utilizes a purified and isolated DNA sequence encoding a peptide with the activities of EPO. The EPO produced by Chugai has biological properties corresponding to those listed in claim 7. (Wall, Tr. 605-606)

574. The Chugai host cells include a DNA sequence encoding for EPO which have been transformed or transfected in a manner allowing them to express biologically active EPO. The Chugai host cells are described by claim 23 of the '008 patent. (Wall, Tr. 606-607)

575. The recombinant EPO expressed by Chugai's host cells is glycosylated. (Wall, Tr. 608)

576. Chugai utilizes eucaryotic, specifically mammalian, host cells in its process of producing recombinant EPO. (Wall, Tr. 609)

577. Claim 28 of the '008 patent describes a biologically functional vector which include the sequences described in claim 7 and is able to encode a biologically active EPO molecule. Claim 28 describes an aspect of the host cell utilized by Chugai. (Wall, Tr. 614)

578. Claim 29 of the '008 patent describes a host cell which is stably transformed or transfected with a DNA vector as described in Claims 28 and 7. (Wall, Tr. 615)

579. Intracellular processes are performed within the Chugai host cell in order to produce recombinant EPO. Unless such intracellular processes are performed, no gene expression occurs, and thus no production of EPO.

These processes are integrated as a combination or set within the host cell. (Wall, Tr. 619)

580. There is no method for making recombinant human EPO other than by use of the host cells claimed in the '008 patent. (Ullrich, Tr. 681)

581. Dr. Sadler, one of Chugai's experts, does not know of any way to make recombinant erythropoietin other than using a recombinant host cell. (Sadler, Tr. 870)

582. In order to not utilize processes within the cells transformed or transfected with the DNA sequence coding for EPO, one would have to avoid using that cell. (Ullrich, Tr. 681-682)

583. The claimed host cell has no practical utility other than to make recombinant erythropoietin. (Rzucidlo, Tr. 1173)

APPENDIX A

Legislative History of 1337a

1. H.R. 5725 was introduced on March 17, 1937 by Rep. Peterson of Florida. The bill, which is as follows, was referred to the House Committee on Ways and Means:

A BILL

To amend the Tariff Act of 1930 to protect against unfair methods of competition and unfair acts in the importation and sale of certain articles and defining certain terms used in connection therewith.

> Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled. That the Tariff Act of 1930, as amended, is amended by inserting after paragraph (h) of section 337 the following paragraph:
>
> When used in this section, the phrase 'unfair method of competition and unfair acts in the importation of articles into the United States, or in their sale by the owner, importer, consignee, or agent of either', shall include, but not by way of limitation, the importation into the United States or the sale by the owner, importer, consignee, or agent of either, of articles or products including combinations or mixtures containing such articles or products, which have been produced or processed in any foreign country as defined in section 336 hereof, under or by means of a process described in any outstanding United States Letters Patent, except where the production or importation of such articles or product is made under license of the registered owner of such patent.

75th Cong., 1st Session.

H. R. 5725 died in Committee without any action on the floor of the House.

2. A) H.R. 7851 was introduced on july 13, 1937 by Rep. Peterson of Florida and referred to the Committee on Patents, with the bill reading as follows:

A BILL

To provide for the protection of certain patent owners, and for other purposes.

> Be it enacted by the Senate and House of Representatives of the united States of america in Congress assembled, That the importation for use, sale or exchange of a product made, produced, or mined under or by means of a process covered by the claims of any outstanding United States letters patent heretofore or hereafter issued except where such articles or products are produced, mined, or processed under authority of the owner of such patent, shall be deemed a violation of the right of the patentee.

75th Cong., 1st Session.

B) Hearings were held on H.R. 7851 on May 5, 1938 by the Subcommittee on Phosphate Rock Process Patents, of the House Committee of Patents. The report on the hearings is entitled "Importation of Goods Covered by United States Patents (Process patents on Phosphate Rock)." Rep. J. Hardin Peterson of Florida, the original sponsor of the bill, testified before the Subcommittee, as did the Secretary of the Manufacturing Chemists' Association, a representative of the Phosphate Rock Institute; the treasurer of the National Fertilizer Association; a representative of the International Agricultural Corporation; and Messrs. Kerkam, Ould, and Finckel, patent attorneys from Washington, D.C., Mr. Finckel being chairman of a committee of the American Patent Law Association. Included in the hearing report is a copy of the decision of In re Amtorg Trading Corporation.

The Chairman of the Subcommittee indicated that Rep. Peterson was a former member of the Committee on Patents and initially read a letter from the Commissioner of Patents stating the Patent Office's position that it would be more appropriate to amend section 337 of the tariff laws than the patent laws. Rep. Peterson stated that he introduced the bills after conferences with both the Chairman of the Tariff Commission and the Commissioner of Patents who both agreed to the need and objective of the legislation, but:

> "The Patent Office takes the position that it should be handled in the Tariff Commission; [while] the Tariff Commission claims that they have no experts on patent matters and that the Patent Office would be best fitted to handle it. I have to have my day in court in some place, so I introduced this bill. ...So that the actual situation is I tried to arrive it by stating it shall be deemed a violation of the rights of the patentee and leaving open the place of enforcement. A violation of the right of a patentee would then become an unfair trade practice, and under the Tariff Act, and the Tariff Commission could exclude such products.

Hearings at 4.

When questioned about whether he had attempted to get his bill (H.R. 5725) to amend the Tariff Act out of the Ways and Means Committee, Rep. Peterson stated yes, but that his handicap was the Chairman of the Tariff Commission insisted they go this way (H.R. 7851) because the Commission had no experts on patent law, and also because the Committee on Ways and Means was tied up with other matters and kept putting the matter off. Hearings at 53-54.

In response to a preliminary question from a committee member on what would be protected by the bill, the chairman stated that the phosphate being imported is covered by an American patent, and Rep. Peterson added that "the bill will cover other products of process patents, as well", and restated that "This bill would protect any industry wherein foreign countries have violated a process patent. In other words, it might be a process affecting matters other than phosphate." Hearings at 5.

In the hearings Rep. Peterson does in very general terms speak about "the distinction between 'process' and 'machine.'" Hearings at 40. Preceding this general discussion Rep. Peterson states the disclaimer:

> Of course the chairman by reason of his long experience on this committee and close study, is far more familiar with the distinctions between process patents and product patents than I am; but the distinction was made, of course, [that] there is protection on product patents, but that protection does not seem to exist where a process is stolen in a foreign country and comes into this country, and the Amtorg case went off on that.
> Hearings at 39.

D) H.R. 7851 died in Committee in the 75th Congress and was not reported out to the floor of the House.

3. A) H.R. 8285 was introduced by Rep. Peterson of Florida on February 2, 1940, 86 Cong. Rec. 1037, and the bill as follows was referred to the House Committee on Mines and Mining:

A BILL

With reference to certain mining practices and defining unfair trade practices in certain instances.

> Be it enacted, etc., That it shall be deemed an unfair trade practice to import for use, sale or exchange any minerals mined, produced or processed by use of the flotation process except where such minerals are produced or mined under authority of the owner of such flotation process.
> Original Text of bill, 86 Cong. Rec. 3783.

B) On March 13, 1940 the Committee on Mines and Mining through Rep. Peterson of Florida, reported on H.R. 8285 with the recommendation that it pass with a Committee amendment which would strike out everything after the enacting clause and substitute the following:

> That it shall be deemed an unfair trade practice and a violation of the right of the patentee, to import for use, sale or exchange any minerals mined, produced, or processed by use of any mining process covered by the claims of any outstanding United States letters patent heretofore or hereafter issued, except where such minerals are produced, processed or mined under authority of the owner of such process.
> H. Report No. 1781, 76th Cong., 3rd Session, March 13, 1940.

The report by Rep. Peterson notes the following:

This bill is designed to correct the present problem which was created when the Court of Customs and Patent Appeals in the case In re Amtorg Trading Corporation reversed its former decisions and held that the importation of products made abroad in accordance with a United States

process patent without consent of patentee was not regarded as an unfair method of competition. The situation created by the Amtorg case was recognized by the United States Tariff Commission in its annual report to Congress in 1935, stating:

> The situation created by this final decision of the court is one that requires the consideration of Congress. The owner of a process patent issued in the United States has now no protection of any kind against the use of that patented process without his consent outside the United States, and importation into and sale within the United States of goods made by the process.

....

> H.R. 7851 was introduced in the Seventy-fifth Congress and extensive hearings were held. H.R. 7851 was broader in scope than this particular bill and was designed to cover all American process patents. The hearings on H.R. 7851 were filed and adopted in part by this committee and what was stated with reference to this bill is equally applicable to the bill under consideration.
>
> A careful study of the testimony previously taken and filed before the Committee shows a clear need for this legislation.
>
> The Joint Congressional Committee to Investigate the Adequacy and Use of the Phosphate Resources of the United States, in its report recommended "that adequate legislation be enacted to protect American process patents." The committee feels that this legislation should pass and that it will be a protection in part to American industry and labor.
>
> The bill being reported out is limited to mining processes. the particular shipment which came into this country was by use of the so-called flotation process which is a an American process, patented.
>
> > Even mining processes perfected by the United States Government and its agencies might be found to be without protection against infringement abroad if the court should continue to hold to the principle laid down in the Amtorg case, unless legislation of this kind is passed.
>
> H. Rep. No. 1781.

C) On April 1, 1940 Rep. Wolcott on the floor of the House offered a substitute for the above committee amendment, and the substitute was agreed to and the title of the bill changed. Rep. Wolcott stated that his prepared amendment would "make it general in character," "to include all articles and products." He stated that "there seems to be no way now, in view of the decision of the Supreme Court in the Mineral case, by which the owner of the patent has any claim against the importer or anyone else." Rep Wolcott indicated t hat Rep. Peterson agreed with the amendment. The changed bill was passed by the House and reads as follows:

> A BILL
>
> To limit the importation of articles, products, and minerals produced, processed, or mined under process covered by outstanding United States patents; to define unfair trade practices in certain instances, and for other purposes.

> That it shall be deemed an unfair trade practice and in violation of the right of the patentee to import for use, sale or exchange any article, mineral, or product produced, processed or mined by use of any process covered by the claims of any outstanding United States letters patent, or to import for use, sale or exchange any article, mineral or product which infringes the right of any patentee under letters patent so issued, except where such articles are product, processed, mined or imported under authority of such process or patent.
>
> 76th Cong., 3rd Session, 86 Cong. Rec. 3782-3783.

D) The House bill was initially referred to the Senate Committee on Mines and Mining, and subsequently ordered transferred to the Senate Committee on Patents for further consideration. 86 Cong. Rec. 7076 (May 29, 1940).

E) On June 19, 1940 the Senate Committee on Patents, chaired by Senator Pepper of Florida, reported on H.R. 8285, recommending that the bill be passed with the following amendment substituting everything after the enacting clause:

A BILL

To limit the importation of products made, produced, processed or mined under process covered by unexpired valid United States patents, and for other purposes.

> That the importation hereafter for use, sale, or exchange of a product made, produced, processed or mined under or by means of a process covered by the claims of any unexpired valid United States letters patent whether issued heretofore or hereafter shall have the same status for the purposes of section 337 of the Tariff Act of 1930 as the importation of any product or article covered by the claims of any unexpired valid United States letters patent.
>
> 76th Cong., 3rd Sess., Sen. Report No. 1903.

The Senate Committee report states that there was filed with the House Committee hearings on H.R. 7851 "a somewhat similar bill designed for the same purpose." Senate Report at 2. The Senate report states that certain changes in the bill were suggested by the Tariff Commission and the changes recommended by the Senate Committee were acceptable to the interested federal agencies. Senate Report at 3-4.

The Senate report described the bill's purpose as follows:

> This bill is designed to correct the present problem which was created when the Court of Customs and Patent Appeals in the case In re Amtorg Trading Corporation reversed its former decisions and held that the importation of products made abroad in accordance with a United States process patent without consent of patentee was not regarded as an unfair method of competition.

Prior to this time such importation had been regarded as an unfair method of competition.

Senate Report at 1-2.

....

Since the Amtorg decision owners of American process patent [sic] are helpless to prevent the infringement abroad of their patent rights. This bill will give to them the same rights which the owners of product patents have. It is felt that the bill is highly desirable and is a protection in part to American industry as well as labor. It also developed at the hearing that even process patents perfected by the United States government and its agencies might be found to be without protection against infringement abroad unless legislation of this kind is passed.

Senate Report at 4.

The above amendment to bill H.R. 8285 was agreed to on the Senate floor and passed by the Senate.

86 Cong. Rec. 8969.

F) On the floor of the House Rep. Peterson asked unanimous consent to take from the Speaker's table H.R. 8285 with the Senate amendments. The Senate amendments were agreed to, there being no objection.

86 Cong. Rec. 9067.

G) H.R. 8285 was approved by the President on July 2, 1940, as follows:

AN ACT

To limit the importation of products made, produced, processed, or mined under process covered by unexpired valid united states patents, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That the importation hereafter for use, sale or exchange of a product made, produced, processed, or mined under or by means of a process covered by the claims of any unexpired valid United States letters patent, whether issued heretofore or hereafter, shall have the same status for the purposes of section 337 of the Tariff Act of 1930 as the importation of any product or article covered by the claims of any unexpired valid United States letters patent.

Public Law No. 710, 76th Cong., 3rd Sess.

CONCLUSIONS OF LAW

1. The U.S. International Trade Commission has jurisdiction over the subject matter of this investigation. FF 2.

2. The claims of the '008 patent do not cover a process. Opn. at 21-15.

3. The '008 patent is not invalid for obviousness. Opn. at 30-35.

4. The '008 patent is not unenforceable for inequitable conduct. Opn. at 55-59.

5. The use of a patented product abroad does not constitute patent infringement. Deepsouth Packing v. Laitram Corp., 406 U.S. 518 (1972).

6. Chugai's use of the '008 patent abroad does not constitute patent infringement. Opn. at 59-61.

7. There is a domestic industry in this investigation under 19 U.S.C. § 1337 (a)(1)(B)(ii) with respect to the articles protected by the '008 patent. Opn. at 61-71.

8. There is no violation of section 337 of the Tariff Act of 1930, as amended, in the importation of certain recombinant erythropoietin, or in its sale, by reason of infringement of U.S. Letters Patent No. 4,703,008. Conclusions of Law 2 - 8.

INITIAL DETERMINATION AND ORDER

Based on the foregoing opinion, findings of fact, conclusions of law, and the record as a whole, and having considered all pleadings and arguments as well as proposed findings of fact and conclusions of law, it is the Administrative Law Judge's INITIAL DETERMINATION (ID) that no violation of § 337 exists in the importation of certain recombinant erythropoietin, or in its sale, by reason of infringement of claims 2, 4-7, 23-25 and 27-29 of U.S. Letters Patent No. 4,703,008.

The Administrative Law Judge hereby CERTIFIES to the Commission this Initial Determination, together with the record of the hearing in this investigation consisting of the following:

1. The transcript of the hearing, with appropriate corrections as may hereafter be ordered by the Administrative Law Judge; and further

2. The exhibits accepted into evidence in this investigation as listed in the attached exhibit lists.

In accordance with Rule 210.44(b), all material found to be confidential by the administrative law judge under Rule 210.6(a) is to be given *in camera* treatment.

The Secretary is instructed to serve a public version of this Initial Determination upon all parties of record and the confidential version upon counsel for complainant Amgen, Inc. and respondents Chugai Pharmaceutical Co., Ltd, Chugai U.S.A., Inc., and The Upjohn Co. who are signatories to the protective order issued by the administrative law judge on February 4, 1988, and the Commission investigative attorney. To expedite service of the public version, counsel is hereby ordered to serve on the

administrative law judge by no later than January 23, 1988, a copy of this Initial Determination with those sections considered by the party to be confidential bracketed in red ink.

This Initial Determination shall become the determination of the Commission 45 days after its date of service unless the Commission within those 45 days shall have ordered review of this Initial Determination, or certain issues herein, pursuant to Rules 210.54(b) or 210.55. 19 C.F.R. § 210.53(h).

Any party to this investigation may request a review by the Commission of this Initial Determination by filing with the Secretary a petition for review, except that a party who has defaulted may not petition for review of any issue regarding which the party is in default. A petition of review shall be filed within ten (10) days after the service of this Initial Determination. 19 C.F.R. § 210.54(a).

Sidney Harris
Administrative Law Judge

Issued: January 10, 1989

PUBLIC VERSION

CONCLUSIONS OF LAW

1. The U.S. International Trade Commission has jurisdiction over the subject matter of this investigation. FF 2.

2. The claims of the '008 patent do not cover a process. Opn. at 21-15.

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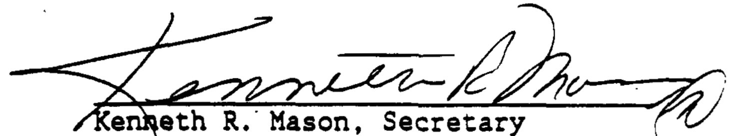
7. There is a domestic industry in this investigation under 19 U.S.C. § 1337 (a)(1)(B)(ii) with respect to the articles protected by the '008 patent. Opn. at 61-71.

8. There is no violation of section 337 of the Tariff Act of 1930, as amended, in the importation of certain recombinant erythropoietin, or in its sale, by reason of infringement of U.S. Letters Patent No. 4,703,008. Conclusions of Law 2 - 8.

CERTIFICATE OF SERVICE

I, Kenneth R. Mason, hereby certify that the attached Initial Determination (Public Version) was served upon Cheri M. Taylor, Esq., and upon the following parties via first class mail, and air mail where necessary, on January 19, 1989.



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