

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS**

AMGEN, INC.,

Plaintiff,

v.

F. HOFFMANN-LA ROCHE, LTD.,
ROCHE DIAGNOSTICS GMBH, and
HOFFMANN-LA ROCHE, INC.

Defendants.

Civil Action No. 05-CV-12237 WGY

**ROCHE'S LIST OF PRIOR ART AND CHART IDENTIFYING CLAIMS BY
CATEGORY REQUESTED BY THE COURT AT THE OCTOBER 4, 2007
AFTERNOON HEARING**

In accordance with the Court's request at the October 4, 2007 afternoon hearing, Roche hereby submits (1) a chart identifying each of the asserted claims as product claims, process claims or product-by-process claims, (2) a list of each of those exhibits that Roche claims to anticipate any of the claims in suit, and (3) a list of all exhibits which constitute prior art in this case.¹

¹ Roche's understanding is that these exhibit lists are intended for the jury. Therefore, Roche has not included on these lists any exhibit relevant only to its contentions of obviousness type double patenting, which the Court has reserved as bench issues. Roche will of course provide those to the Court if it desires.

CLAIM CHART

| | Product | Process | Product by Process |
|------|---|---|---------------------------|
| '868 | | 1 and 2 | |
| '698 | | 6-9 | |
| '349 | | 7 | |
| '933 | 9, 12 (each depending from product by process claims) | 11 and 14 (each depending from product by process claims) | 3, 7, 8 |
| '422 | 1 | | |

Roche notes that Amgen has no objections to the claim chart, with the exception that Amgen stylizes '933 claims 11 and 14 as "methods for treating" claims. Whether stylized in this manner or not, such claims are therefore clearly process claims, which depend from product-by-process claims.

ANTICIPATORY PRIOR ART

(Amgen disputes each of the exhibits Roche identified as being anticipatory prior art)

| Prior art publications demonstrating anticipation under 35 U.S.C. §§102(a) or (b) | |
|---|--|
| TRX | DESCRIPTION |
| 2002 | Miyake et al, "Purification of Human Erythropoietin", J. Biol. Chem. 252(15): 5558-64 (1977) |
| 2088 | Goldwasser Grant Application re Erythropoietin: Purification Properties Biogenesis (1979) |
| 0019 2049 2049A 2050 | Documents from Dr. Baron (Clinical Trial Data, 1979-1980 with human urinary erythropoietin) |
| 2004 | IND/NDA Subsequent Submissions Review Transmittal to M. Peterson from J. Baron (IND submitted 2/3/79) |
| 2045 | Grant Application: Erythropoietin: Purification, Properties, Biogenesis (August 1984) |
| 0008 0009 | Letter from Baron to Temple (FDA) Enclosing Materials for a Physician Sponsored IND for Human EPO |
| 2060 2068 2079 | Egrie et al, "Characterization of Recombinant Human and Monkey Erythropoietin" Abstract from 10th Annual Fredrick Stohlman Memorial Symposium on Stem Cell Physiology, Boston, MA (1984) |
| 2051 | Essers, U., et al., "Effect of Erythropoietin in healthy subjects and in patients with chronic uremia" Klin. Wschr., 1973, 51:1005-1009 with certified translation |
| 2052 | Essers et al, "Weitere Untersuchungen zur Wirksamkeit von Erythropoetin bei Patienten mit Nierensuffizienz," 1614-1624 (1974) |
| 2053 | Essers et al, "Effect of Erythropoietin in Normal Men and in Patients with Renal insufficiency" European Dial. and Trans. Proceedings 2: 398-402 (1975) |

Exhibits relating to the Eschbach human trial providing evidence of anticipation under 35 U.S.C. §§102(g)(2)(prior invention) or under §§102(a) or (b)(prior public knowledge or use)

| TRX | DESCRIPTION |
|------|--|
| 0020 | Human patient trial with human erythropoietin; Eschbach et al., "Correction of the Anemia of End-Stage Renal Disease with Recombinant Human Erythropoietin," New England Journal of Medicine, 316:73-78 (Jan. 8, 1987) |

Additional exhibits relating to the Goldwasser Clinical Trial providing evidence of anticipation under 35 U.S.C. §§102(a) or (b)(prior public knowledge or use), or under §§102(f) or (g)(2)(prior invention)

| TRX | DESCRIPTION |
|------|---|
| 2043 | Grant Application: Re: Erythropoietin, Purification, Properties, Biogenesis |
| 2054 | Proposed protocol for the r-HuEPO Phase I study |

| Exhibits relating to Dr. Fritsch's cloning and expression of rhEPO providing evidence of anticipation under 35 U.S.C. §§102(g)(2)(prior invention) | |
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| TRX | DESCRIPTION |
| 2012.164 | Jacobs (1985) Isolation and Characterization of Genomic and cDNA Clones of Human Erythropoietin [at AM-ITC 000164 – 000168] |
| 2084 | Notebook 193 (Edward Fritsch) |
| 2090 | Collaboration Agreement between T. Miyake and Genetics Institute (signed) |

PRIOR ART**(Exhibits Amgen disputes as constituting prior art are indicated by (*))**

| TRX | DESCRIPTION |
|------------|--|
| 2024 | Axel U.S. 4,399,216 |
| 2026 | McCormick 06/438,991 (File History for U.S. 4,966,843) |
| 2027 * | McCormick U.S. 4,966,843 (102(e) prior art for all subject matter disclosed in McCormick 06/438,991) |
| 2028 | EP 0 088 540 A2 |
| 2029 | EP 0 093 619 A1 |
| 2030 | Goeddel U.S. 4,766,075 |
| 2034 | Alton WO 83/04053 |

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| 0008 * | Letter from Baron to Temple (FDA) Enclosing Materials for a Physician Sponsored IND for Human EPO |
| 0009 * | Letter from Baron to Temple (FDA) Enclosing Materials for a Physician Sponsored IND for Human EPO |
| 0010 | Maniatis et al., "Molecular Cloning - A Laboratory Manual," Cold Spring Harbor Laboratory (1982) |
| 0011 | "Genentech readies trials for TPA, gamma interferon," McGraw-Hill's Biotechnology Newswatch. |
| 0012 | Sue and Sutkowski, "Site-specific antibodies to human erythropoietin directed toward the NH2-terminal region," <i>Proc Natl Acad Sci USA</i> 80: 3651-3655 (1983) |
| 0013 | Chiba U.S. Patent 3,865,801 for Stabilization of Urinary Erythropoietin Using Sodium P-Aminosalicylate and Extracting into Phenol |
| 0014 | Lee-Huang, S. (1980) "A New Preparative Method for Isolation of Human Erythropoietin With Hydrophobic Interaction Chromatography," <i>Blood</i> , 56(4), 620, 622, and 624 (Oct. 1980) |
| 0019 * | Summary Sheet of Patient Data for all Three Patients |
| 0020 * | Eschbach et al., "Correction of the Anemia of End-Stage Renal Disease with Recombinant Human Erythropoietin," <i>New England Journal of Medicine</i> , 316:73-78 (Jan. 8, 1987) |
| 0022 * | Excerpt from "Notice of Grant Award" to Dr. David Nathan (AM-ITC-00260506 - AM-ITC-00260507) |
| 0027 * | 2/15/1983 Memo from Fred Morris re: February 3, 1983 RMG Review of EPO Project |
| 0039 | Konrad M et al. Applications of genetic engineering to the pharmaceutical industry. <i>Ann N Y Acad Sci.</i> 1983;413:12-22. |
| 0041 | Goldwasser E et al., "On the mechanism of erythropoietin-induced differentiation: XIII. The role of sialic acid in erythropoietin action," <i>J. Biol. Chem.</i> 249(13):4202-6 (1974) |
| 0042 * | Hagiwara et al., "Erythropoietin Production in a Primary Culture of Human Renal Carcinoma Cells Maintained in Nude Mice," <i>Blood</i> , Vol. 63, No. 4, :pp. 828-835 (April 1984) |
| 0043 | Lodish, "Post-translational modifications of proteins," <i>Enzyme Microb Technol</i> 3:178-88 |
| 0049 | Fisher, J., MiniReview "Control of Erythropoietin Production," <i>Pro. Soc. Exp. Biol. Med.</i> 173: 289-305 (1983) |

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| 2001 | Haynes and Weissmann, "Constitutive, long-term production of human interferons by hamster cells containing multiple copies of a cloned interferon gene," Nucleic Acid Res. 11: 687-706 (1983) |
| 2002 | Miyake et al, "Purification of Human Erythropoietin", J. Biol. Chem. 252(15): 5558-64 (1977) |
| 2004 * | IND/NDA Subsequent Submissions Review Transmittal to M. Peterson from J. Baron (IND submitted 3/2/79) |
| 2005 * | Letter to F. Gaylis from J. Egrie RE: EPO RIA samples |
| 2010 | Hunkapiller and Hood, "Protein Sequence Analysis: Automated Microsequencing," Science 219: 650-659 (1983) |
| 2012.164* | Jacobs (1985) Isolation and Characterization of Genomic and cDNA Clones of Human Erythropoietin [at AM-ITC 000164 – 000168] |
| 2012.260* | Collen (1984) Biological Properties of Human Tissue-Type Plasminogen Activator Obtained by Expression of Recombinant DNA in Mammalian Cells, J. of Pharmacology and Exp. Therapeutics, 231(1), 146-152 (1984) [at AM-ITC 00454391 – 00454397] |
| 2013.317 | Chirgwin (1979) Isolation of Biologically Active RNA from Sources Enriched in Ribonuclease," Biochemistry, 18(24), 5294-5299 (1979) [at AM-ITC 00448184 – 00448189] |
| 2018 | Hunkapiller, "New Protein Sequenator with Increased Sensitivity," Science 207(1): 523-525 (1980) |
| 2019 | Goeddel et al, "Expression in Escherichia Coli of chemically synthesized genes for human insulin," PNAS 76: 106-110 (1979) |
| 2020 | Gething and Sambrook, "Cell surface expression of influenza haemagglutinin from a cloned DNA copy of the RNA gene," Nature 293: 620-625 (1981) |
| 2021 | Suggs et al, "Use of Synthetic Oligonucleotides as hybridization probes: Isolation of cloned cDNA sequences for human b2-microglubin," PNAS 78: 6613-17 (1981) |
| 2022 | Kornblihtt et al, "Isolation and characterization of cDNA clones for human and bovine fibronectins," Proc Natl Acad Sci 80: 3218-3222 (1983) |
| 2023 | Farber and Zanjani, "Translation of mRNA from Human Kidneys into Biologically Active Erythropoietin Following Microinjection into Xenopus Laevis Oocytes," Clinical Res. 31: 769A (1983) |
| 2025 | Kaufman and Sharp, "Construction of a Modular Dihydrofolate Reductase cDNA Gene: Analysis of Signals Utilized for Efficient Expression," Mol. Cell. Biol. 2: 1304-1319 (1982) |
| 2031 | Remington's Pharmaceutical Sciences, 16th ed. A Osol (ed.) Easton, Pennsylvania, Mack Publishing (1980) |
| 2032 * | Eschbach et al, "The Anemia of Chronic Renal Failure in Sheep," Clin Invest 74: 434-441 (1984) |
| 2033 | Goldwasser and Kung, "Purification of Erythropoietin," PNAS 68: 697-98 (1971) |
| 2038 * | Letter from Goldwasser to Mach |
| 2040 * | Letter to E. Goldwasser from A. Mendelson RE: missing docs from SAB and Major Consultants Confidentiality Agreements |
| 2041 * | Letter to E. Goldwasser from N. Stebbing RE: Erythropoietin update |
| 2042 * | Letter to N. Stebbing from E. Goldwasser RE: EPO-Program update |
| 2043 * | Grant Application: Re: Erythropoietin, Purification, Properties, Biogenesis |
| 2044 * | Letter from D. Vapnek to E. Goldwasser re grant application |
| 2045 * | Grant Application: Erythropoietin: Purification, Properties, Biogenesis |

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| 2048 | Dordal, "The Function and Composition of the Carbohydrate Portion of Human Urinary Erythropoietin," UMI Dissertation Services |
| 2049 * | Documents from Dr. Baron |
| 2049A * | Patient Horizontal Graphs for all 3 patients |
| 2050 * | Clinical Study of Purified Human Erythropoietin (1979-1980) |
| 2051 * | Essers, U., et al., "Effect of Erythropoietin in healthy subjects and in patients with chronic uremia" Klin. Wschr., 1973, 51:1005-1009 with certified translation |
| 2052 * | Esser et al, "Weitere Untersuchungen zur Wirksamkeit von Erythropoetin bei Patienten mit Nierensuffizienz," 1614-1624 (1974) |
| 2053 * | Essers et al, "Effect of Erythropoietin in Normal Men and in Patients with Renal insufficiency" European Dial. and Trans. Proceedings 2: 398-402 (1975) |
| 2054 * | Proposed protocol for the r-HuEPO Phase I study |
| 2055 * | Letter to E. Esber from S. Ronspies RE: Submission of product license application for Activase (Excerpt: ROCHE-GNE- 03009, 03050, 03054, 03059) |
| 2060 * | Egrie et al, "Characterization of Recombinant Human and Monkey Erythropoietin" Abstract from 10th Annual Fredrick Stohlman Memorial Symposium on Stem Cell Physiology, Boston, MA (1984) |
| 2064 * | Memorandum to G. Rathman from D. Vapnek RE: Summary of EPO Discussion with Kirin |
| 2066 * | Memorandum to G. Binder from J. Egrie and J. Fenno RE: Summary of Erythropoietin Clinical Panel Meeting |
| 2068 * | Egrie et al, "Characterization of Recombinant Human and Monkey Erythropoietin" Abstract from 10th Annual Fredrick Stohlman Memorial Symposium on Stem Cell Physiology, Boston, MA (1984) |
| 2071 * | Egrie Laboratory Notebook No. 448 |
| 2072 * | Letter from Egrie to Gaylis re Finally Finished the EPO RIAs on Last Set of Samples Sent |
| 2073 | E. Goldwasser & J. Sherwood, "Annotation Radioimmunoassay of Erythropoietin," Brit. J. Haematol., 48:359-363 (1981) |
| 2075 | Ascensao et al, "Erythropoietin Production by a Human Testicular Germ Cell Line," Blood 62(5): 1132-34 (1983) |
| 2076 | Beaucage et al. (1981) "Deoxynucleoside Phosphoramidites--A new Class of Key Intermediates for Deoxypolynucleotide Synthesis," Tetrahedron Letters, 22(20), 1859-1862 (1981) |
| 2077 | Edge et al, "Total synthesis of a human leukocyte interferon gene," Nature 292(5825): 756-62 (1981) |
| 2078 | Edge, M.D., et al. (1983) "Chemical synthesis of a human interferon-alpha 2 gene and its expression in Escherichia coli," Nucleic Acids Res. 11(18):6419-35 (1983) |
| 2079 * | Egrie et al, "Characterization of Recombinant Human and Monkey Erythropoietin" Abstract from 10th Annual Fredrick Stohlman Memorial Symposium on Stem Cell Physiology, Boston, MA (1984) |
| 2080 | Farber and Zanjani, "Translation of mRNA from Anemic Baboon Kidney into Biologically Active Erythropoietin," Exp Hematol. 11 (S14): 57 (1983) |
| 2081 | Glanville et al, "Completion of the amino acid sequence of the $\alpha 1$ chain from type I calf skin collagen," The Biochem. J. 215: 183-189 (1983) |
| 2082 | Sherwood and Goldwasser, "A radioimmunoassay for erythropoietin," Blood 54 (4): 885-893 (1979) |
| 2084 * | Notebook 193 (Edward Fritsch) |

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| 2085 * | Memorandum to J. Fenno, N. Stebbing from D. Vapnek RE: IND |
| 2088 * | Goldwasser Grant Application re Erythropoietin: Purification Properties Biogenesis |
| 2090 * | Collaboration Agreement between T. Miyake and Genetics Institute (signed) |
| 2091 * | Memorandum to J. Fenno and N. Stebbing from D. Vapnek RE: IND for EPO |
| 2093 * | Molecular Cloning and Characterization of the Gene Encoding Erythropoietin, Daniel Vapnek |
| 2095 | Farber and Zanjani, "Translation of mRNA from Human Kidneys into Biologically Active Erythropoietin Following Microinjection into Xenopus Laevis Oocytes," Blood 62(5) (Supp. 1):122a, Abstract No. 392 (1983) |
| 2097 * | Notice of Grant Award - The Developmental Biology of Human Erythropoiesis from 07.01.81-06.30.86 (renewal) |
| 2098 * | Orkin S.H., et. al., Molecular cloning of human adenosine deaminase gene sequences. J. Biol. Chem., 258:12753-12756 |
| 2099 | Michelson, A.M., et al., Isolation of DNA sequence of a full-length cDNA clone for human X chromosome-encoded phosphoglycerate kinase. J. Biol. Chem., 80: 472-476, 1983 |
| 2100 * | Notice of Grant Award - The Developmental Biology of Human Erythropoiesis from 07.01.81-06.30.86 |
| 2101 | Lawn et al. (1978) "The Isolation and Characterization of Linked delta- and beta-Globin Genes from a Cloned Library of Human DNA," Cell, 15, 1157-1174 (Dec. 1978) |
| 2102 | American Type Culture Collection ("ATCC"), Catalogue of Cell Lines, Viruses, and Antisera, 4th ed. (1983) |
| 2103 | Wallace et al, "The use of synthetic oligonucleotides as hybridization probes. II Hybridization of oligonucleotides of mixed sequence to rabbit alpha-globin DNA," Nucleic Acids Res. 9(4): 879-894 (1981) |
| 2104 | Urlaub and Chasin, "Isolation of Chinese hamster cell mutants deficient in dihydrofolate reductase activity," PNAS 77: 4216-4220 (1980) |

The above lists were prepared in response to the Court's request for Trial Exhibits.² Testimony of witnesses at trial also constitutes relevant evidence of Roche's prior art defenses under various sections of 35 U.S.C. §§102 and 103.

DATED: October 10, 2007

F. HOFFMANN-LA ROCHE LTD,
 ROCHE DIAGNOSTICS GMBH,
 and
 HOFFMANN-LA ROCHE INC.

² In that the case is still proceeding, Roche reserves the right to supplement to conform to any evidence later adduced at trial

By its attorneys,

/s/ Vladimir Drozdoff

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CERTIFICATE OF SERVICE

I hereby certify that this document filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF). Pursuant to agreement of counsel dated September 9, 2007, paper copies will not be sent to those indicated as non registered participants.

/s/ Vladimir Drozdoff
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