Exhibit 7

Declaration of Krista M. Rycroft in Support of Roche's Motion for Summary Judgment that Claim 1 of the '422 Patent Is Invalid Under 35 U.S.C. § 112

03099/00501 689819.1

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1900 Oak Terrace Lane/Thousand Oaks, California 91320-1789/Telephone 805 499-5725

September 27, 1985

James T. Fenno
Director, Regulatory Affairs

Elaine Esber, M.D.
Director
Office of Biologics Research and Review
Center for Drugs and Biologics
Food and Drug Administration
8800 Rockville Pike
Bethesda, Maryland 20205

Dear Dr. Esber:

Amgen is forwarding three copies of its Notice of Claimed Investigational Exemption for a New Drug, Recombinant-Human Erythropoietin (r-HuEPO). The initial intended use of this product is as a parenteral treatment for anemia associated with renal disease.

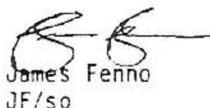
Included as Item 5S of this submission is the release protocol for r-HuEPO lot 502H5. As additional lots are prepared for clinical evaluation, release protocols for those lots will be submitted to your office. Drs. J. Adamson and J. Eschbach, the co-principal investigators for the initial clinical study with end stage renal disease patients at the University of Washington, will utilize lot 502H5.

At this time, the IRB which has jurisdiction over the study institution has not completed its review. The study will not commence prior to gaining IRB approval, and such written authorization will be forwarded to your office when as it is received.

We have stamped as confidential those pages which contain information which Amgen considers to be proprietary in nature, and we request that such pages be withheld from disclosure to third parties.

If you have any questions concerning this submission, please contact me or Larry Johnson at (805) 499-5725.

Sincerely yours,



James Fenno
JF/so

Attachment: 3 copies of Notice of Claimed Investigational Exemption for a New Drug, Recombinant-Human Erythropoietin

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved OMB No. 0910-0014

NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION FOR A NEW DRUG

NOTE: No drug may be shipped or study initiated unless a complete statement has been received. (21 CFR 312.1(a)(2)).

Name of Sponsor Amgen Date Sept. 27, 1985

Address 1900 Oak Terrace Lane, Thousand Oaks, CA 91320 Telephone (805) 499-5725

Name of Investigational Drug Recombinant-Human Erythropoietin (r-HuEPO)

FOR A DRUG:

Food And Drug Administration
Office of New Drug Evaluation *(HFN-106)*
5600 Fishers Lane
Rockville. Maryland 20857

FOR A BIOLOGIC:

Food and Drug Administration
Office of Biologics *(HFN-823)*
8800 Rockville Pike
Bethesda, Maryland 20205

Dear Sir:

The sponsor, Amgen, submits this notice of claimed investigational exemption for a new drug under the provisions of section 505(i) of the Federal Food. Drug, and Cosmetic Act and § 312.1 of Title 21 of the Code of Federal Regulations.

Attached hereto in triplicate are:

1. The best available descriptive name of the drug, including to the extent known the chemical name and structure of any new-drug substance, and a statement of how it is to be administered. (If the drug has only a code name, enough information should be supplied to identify the drug.)

2. Complete list of components of the drug, including any reasonable alternates for inactive components.

3. Complete statement of quantitative composition of drug, including reasonable variations that may be expected during the investigational stage.

4. Description of source and preparation of any new-drug substances used as components, including the name and address of each supplier or processor, other than the sponsor, of each new-drug substance.

5. A statement of the methods, facilities, and controls used for the manufacturing, processing, and packing of the new drug to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for safety and to give significance to clinical investigations made with the drug.

6. A statement covering all information available to the sponsor derived from preclinical investigations and any clinical studies and experience with the drug as follows:

a. Adequate information about the preclinical investigations, including studies made on laboratory animals, on the basis of which the sponsor has concluded that it is reasonably safe to initiate clinical investigations with the drug: Such information should include identification of the person who conducted each investigation; identification and qualifications of the individuals who evaluated the results and concluded that it is reasonably safe to initiate clinical investigations with the drug and a statement of where the investigations were conducted and where the records are available for inspection; and enough details about the investigations to permit scientific review. The preclinical investigations shall not be considered adequate to justify clinical testing unless they give proper attention to the conditions of the proposed clinical testing. When this information, the outline of the plan of clinical pharmacology, or any progress report on the clinical pharmacology, indicates a need for full review of the preclinical data before a clinical trial is undertaken, the Department will notify the sponsor to submit the complete preclinical data and to withhold clinical trials until the review is completed and the sponsor notified. The Food and Drug Administration will be prepared to confer with the sponsor concerning this action.

b. If the drug has been marketed commercially or investigated (e.g. outside the United States), complete information about such distribution or investigation shall be submitted, along with a complete bibliography of any publications about the drug.

c. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of preexisting information from preclinical and clinical investigations and experience with its components, including all reports available to the sponsor suggesting side-effects, contraindications, and ineffectiveness in use of such components: Such summary should include an adequate bibliography of publications about the components and may incorporate by reference any information concerning such components previously submitted by the sponsor to the Food and Drug Administration. Include a statement of the expected pharmacological effects of the combination.

d. If the drug is a radioactive drug, sufficient data must be available from animal studies or previous human studies to allow a reasonable calculation of radiation absorbed dose upon administration to a human being.

7. A total (one in each of the three copies of the notice) of all informational material, including label and labeling, which is to be supplied to each investigator: This shall include an accurate description of the prior investigations and experience and their results pertinent to the safety and possible usefulness of the drug under the conditions of the investigation. It shall not represent that the safety or usefulness of the drug has been established for the purposes to be investigated. It shall describe all relevant hazards, contraindications, side-effects, and precautions suggested by prior investigations and experience with the drug under investigation and related drugs for the information of clinical investigators.

8. The scientific training and experience considered appropriate by the sponsor to qualify the investigators as suitable experts to investigate the safety of the drug, bearing in mind what is known about the pharmacological action of the drug and the phase of the investigational program that is to be undertaken.

9. The names and a summary of the training and experience of each investigator and of the individual charged with monitoring the progress of the investigation and evaluating the evidence of safety and effectiveness of the drug as it is received from the investigators, together with a statement that the sponsor has obtained from each investigator a completed and signed form, as provided in subparagraph (12) or (13) of this paragraph, and that the investigator is qualified by scientific training and experience as an appropriate expert to under-

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DATA TO SUPPORT A
NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION
FOR
RECOMBINANT-HUMAN ERYTHROPOIETIN
(r-HuEPO)

September 27, 1985

Amgen
1900 Oak Terrace Lane
Thousand Oaks, CA 91320

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CONFIDENTIALITY STATEMENT

Certain information and data contained in this Notice of Claimed Investigational Exemption for a New Drug are confidential. Pages containing such information are so marked. The Food and Drug Administration shall regard this confidential information in accordance with the provisions of 21 CFR 312.5 and 21 CFR 314.14.

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nucleotide sequence were compared with the amino acid sequence of mature human urinary EPO. From this data the coding segments (exons) of the gene were identified. In addition, comparison of the EPO genomic sequence to the M-cDNA sequence and to the HuEPO DNA sequence derived from mRNA isolated as described in Item 4A of this Notice confirmed the intron-exon junction assignments. Each intron-exon junction conforms to consensus splice rules (Mount, 1982). The exons are displayed in Figure 4A-7 with the deduced amino acid sequence listed above each exon.

The organization of the human EPO gene is described in Item 4A of this Notice. The sequence downstream of the polyadenylation site does not contain any significant open reading frames. Each frame is closed by closely-spaced termination codons. The largest open region contains 124 codons. A large direct repeat is found in the 1.8 kb SstI - SstI fragment at the 3' end of the sequence. These repeated sequences are approximately 401 bases long.

Protein Sequence Conforms

Complete amino acid sequence determination of purified r-HuEPO produced by the production cell line MWCB 51B was performed to support verification of the r-HuEPO coding region. The DNA and protein sequence information verify the integrity of the coding regions within the production strain. The status of complete sequence determination is shown in Figure 4B-6 which also indicates amino acid sequence determination of peptides derived from r-HuEPO.

Intact r-HuEPO was analyzed by automated Edman degradation using a

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gas-phase sequencer (Hewich et al., 1981 and Lai, 1984) through 50 cycles. PTH-amino acids were analyzed by reverse phase HPLC (Hunkapiller et al., 1983). A single sequence could be assigned for the N-terminal 45 residues. No PTH-amino acid was identified for positions 7, 24, 29, 33, and 38. Positions 24 and 38 were assigned glycosylated asparagines according to the rule of N-glycosylation (Asn-X-Ser/Thr) and the evidence that glucosamine was found in the hydrolysates of S. aureus protease peptides S-38 and S-59. Positon 7 was later assigned as cysteine residue from sequence analysis of peptides S-39a and S-39b.

Further sequence information of r-HuEPO was obtained from sequence analysis and/or amino acid composition of peptide derived from protease digests of r-HuEPO using TPCK-treated trypsin or S. aureus V8 protease. In most cases, peptide samples were sequenced to the C-terminal end. Sequences obtained from these peptides were used in the reconstruction and overlapping of the entire amino acid sequence for r-HuEPO. As shown in Figure 4B-6, 163 of 166 amino acid residues of purified r-HuEPO were sequenced at least once by Edman degradation. The remaining three at positions 29, 33 and 166 were assigned as described below.

Cys 29 and Cys 33 were tentatively assigned according to the amino acid sequence deduced from DNA sequence analysis. The C-terminal residue, Arg 166, was sequenced by the method of carboxypeptidase digestion. In addition, position 83 was assigned as a glycosylated asparagine according to the sequencing results (PTH-amino acid could not be identified), the rule of N-glycosylation (Asn-X-Ser/Thr), and the

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evidence that glucosamine was found in the hydrolysates of peptides S-64 and T-59. Position 126 was assigned as a O-glycosylated serine according to the sequencing results (no PTH-amino acid could be identified from sequence analysis of peptide S-49), and amino acid composition analysis of peptide S-49 which indicated the presence of two serine residues and galactosamine. Two peptide bonds, Lys 116-Glu 117 and Asp 165-Arg 166, need to be further confirmed to provide necessary overlapping information for peptides T-9 and T-41a, and for overlapping of S-39B or T-4a with the C-terminal sequence.

Amino Acid Sequence of Human Urinary Derived Erythropoietin

The complete amino acid sequence of urinary (natural) human erythropoietin has also been determined. Purified material (Miyake *et al*., 1977) for analysis was provided by Dr. Eugene Goldwasser, University of Chicago, Chicago, IL.

Purified EPO was separately subjected to three different protease digestions using TPCK-treated trypsin for two digests (the first in 10 m*M* $CaCl_2$, 0.1 *M* Tris-HCl, pH 8.0, the second in 0.1 *M* ammonium bicarbonate, pH 8.0) and *S. aureus* V8 protease for the third sample. All samples were separated by reverse-phase HPLC immediately following digestion. Peptides were eluted by a gradient of an organic mobile phase (TFA) in an aqueous mobile phase (TFA plus acetonitrate). Fractions were manually collected, dried, and kept at -20°C.

Automated sequence analysis (Hewick *et al*., 1981 and Lai, 1984) of intact proteins and peptide fragments isolated by HPLC were performec

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with a gas-phase sequenator. In situ CNBr cleavage of the remainder of the protein molecule following extended sequence analysis of the intact protein was performed using 70% CNBr in formic acid. All peptide solutions were made in 50% formic acid in water prior to application to the sequenator. The PTH-amino acid obtained from each sequenator cycle was identified by reverse-phase HPLC (Hunkapiller et al., 1983). PTH-cysteinyl residues were identified as PTH-cysteic acid residues by reverse-phase HPLC on a C18 column (Rainin) after oxidation of the Edman degradation product with performic acid at 0°C.

The complete amino acid sequence for the human urinary-derived EPO protein in shown in Figure 4B-7. The sequenced region of the intact protein and the various fragments used to establish the order of sequences obtained by cleavage of the protein are also indicated. About 30 - 80% of the peptide samples obtained in each fraction were sequenced.

All of the residues were assigned positions by sequencing, except the asparagines at positions 24, 38 and 83, and one cysteine at position 161. DNA sequence analysis has assigned three glycosylation sites at positions 24, 38 and 83, according to the rule of Asn-X-Ser/Thr. Subsequent carbohydrate analysis (described elsewhere in Item 5 of this Notice) has confirmed these glycosylation events. Glycosylated asparagines are not detectable by this sequencing method.

These results demonstrate that the amino acid sequence of natural (urine derived) human erythropoietin and r-HuEPO are identical, and that both conform to the amino acid sequence deduced from DNA sequence analysis of the gHuEPO clone.

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FIGURE 4B-6

Amino acid sequence of r-HuEPO. Shown is the amino acid sequence of purified r-HuEPO obtained by automated Edman degradation of the intact protein and/or peptides derived from trypsin or V8-protease digests. Amino acid composition and/or sequential Edman degradation was used to define peptide sequences. (See Item 4B for a more complete description of the methods employed.)

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FIGURE 4B-6

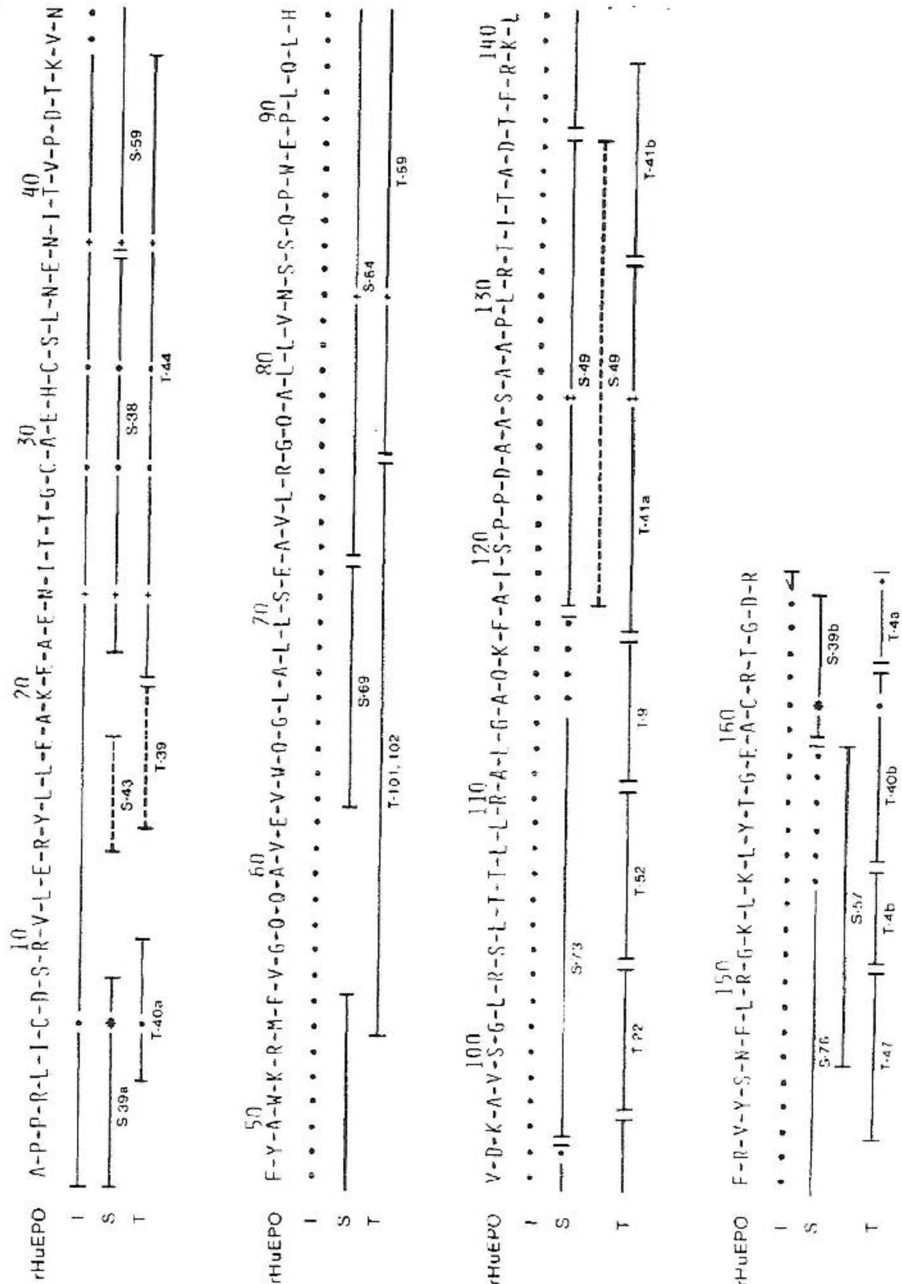

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FIGURE 4B-7

Amino acid sequence of human urinary-derived erythropoietin. Shown is the amino acid sequence of purified human urinary-derived erythropoietin obtained by automated Edman degradation of the intact protein and/or peptides derived from trypsin or V8-protease digests. Amino acid composition and/or sequential Edman degradation was used to define peptide sequences. (See Item 4B for a more complete description of the methods employed.)

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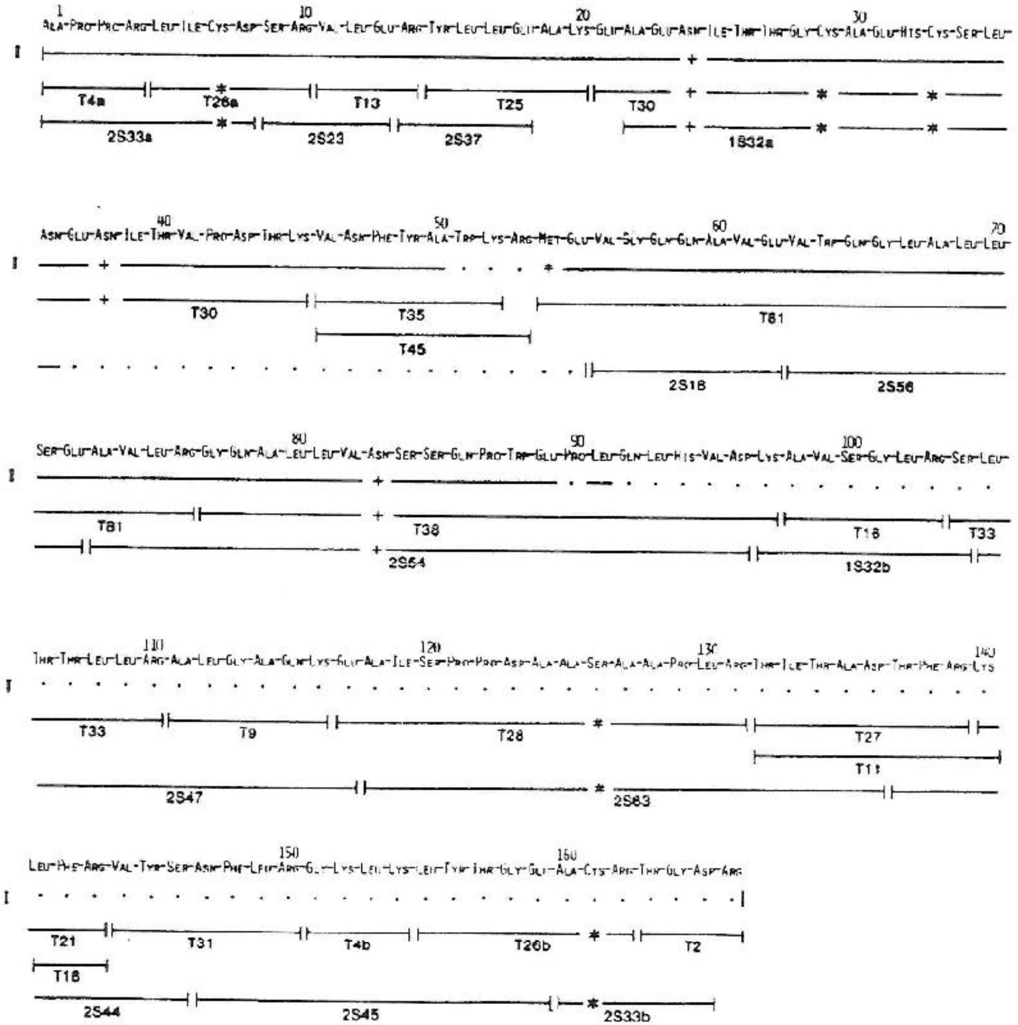
FIGURE 4B-7



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