EXHIBIT 4
PRODUCT LICENSE APPLICATION

Recombinant Human Erythropoietin
(r-HuEPO)

October 30, 1987

Amgen, Inc.
1900 Oak Terrace Lane
Thousand Oaks, CA 91320

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AMGEN CONFIDENTIAL BUSINESS INFORMATION
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9. FINAL PRODUCT CHARACTERIZATION

A. Summary

Biochemical and biophysical analyses, were performed to define r-HuEPO's chemical composition (e.g., amino acid analysis, peptide mapping, amino acid sequence) and physical properties (e.g., by defining Stokes radius, molecular weight, solution shape, secondary and tertiary structure, fluorescence spectroscopy, and phosphorescence quenching). Where it was possible to compare r-HuEPO and u-HuEPO, the two materials were shown to be identical within the error of the methods.

Carbohydrate analysis of r-HuEPO and u-HuEPO was performed by compositional analysis, enzyme digestion, and sequence analysis. No significant differences were found. The most relevant findings were the overall similarity of the oligosaccharide structures and the demonstration that all of the carbohydrate structures in r-HuEPO are also found in u-HuEPO.

The biological and immunological properties of erythropoietin were evaluated by in vivo bioassays, in vitro bioassays, and immunological assays. All such characterization studies indicate that r-HuEPO and u-HuEPO are indistinguishable in their biological and immunological properties. Both materials were found to influence megakaryocyte development in vitro, but...
neither had any effect on the development of stem cells, very early erythroid progenitor cells, or other cells in the myeloid lineage.

Process characterization studies demonstrate the reproducibility and resilience of the r-HuEPO manufacturing process. The purification process effectively eliminates DNA, proteins, and small molecule contamination from r-HuEPO-containing cell-conditioned media and, in challenge studies, destroyed a wide variety of test viruses. r-HuEPO investigational lots have demonstrated a constant specific activity and consistent carbohydrate structure. The cell line engineered to contain the erythropoietin gene has been shown to be genetically stable and to consistently produce r-HuEPO in the cell culture process.
B. Physical Properties of Erythropoietin

1. Summary

In order to more fully define its molecular characteristics, r-HuEPO was subjected to analysis by several biochemical and biophysical techniques. The chemical composition of r-HuEPO was characterized by determination of the complete amino acid sequence, tryptic peptide mapping, amino acid analysis, and C-terminal analysis. Determination of the carbohydrate structure is described in Section 9.C. Sedimentation equilibrium studies using the analytical ultracentrifuge were performed to determine the molecular weight and confirm the purity of r-HuEPO. In conjunction with an estimate of the Stokes radius by analytical gel filtration, the sedimentation data allows the prediction of a solution shape for r-HuEPO. Analysis by circular dichroic spectroscopy indicates that r-HuEPO possesses a defined tertiary structure and allows the estimation of the amount of secondary structure present. Fluorescence and phosphorescence spectroscopy and quenching experiments were used to probe the local environment of tryptophan residues in r-HuEPO. The extinction coefficient was derived by dry weight determination.
u-HuEPO was also analyzed by many of the same techniques, although the scarcity of this material did not permit as complete an examination as was possible with r-HuEPO. The physical properties of r-HuEPO are, within the error of the methods of analysis, indistinguishable from those of u-HuEPO. Only in the case of the fine structure of the carbohydrate moieties (Section 9.C) can a distinction between r-HuEPO and u-HuEPO be defined. Even this difference is quantitative rather than qualitative. While the relative proportions of the carbohydrate moieties are somewhat different, all of the carbohydrate structures found in r-HuEPO are also found on u-HuEPO.

A description of the methods employed, as well as the results obtained with r-HuEPO and u-HuEPO, are described.
2. Primary Amino Acid Sequence

a. Sequence Analysis of r-HuEPO

The primary amino acid sequence of r-HuEPO was determined by automated Edman degradation (using a gas phase sequenator) of intact protein and peptide fragments, and by amino acid compositional analysis of peptide fragments. The PTH-amino acid obtained from each sequenator cycle was identified by reversed phase HPLC. The r-HuEPO molecule contains two disulfide bonds, Cys 7-Cys 161 and Cys 29-Cys 33, and four glycosylation sites at Asn 24, Asn 38, Asn 83 and Ser 126.

Peptide fragments were generated by digestion of r-HuEPO with either trypsin, S. aureus V8 protease, or endo lys-C protease and then separated by C4 reversed phase HPLC. Figures 9.8-1, 9.8-2 and 9.8-3 show the peptide maps and the digestion conditions. The results of the complete amino acid sequence determination are shown in Figure 9.8-4, which also shows the amino acid sequence determination of each peptide fragment derived from r-HuEPO. Overlapping peptide fragments were used in the sequence determination.

Since cysteine residues are not detected by the sequencing method, the positions of the cysteines and the disulfide
bonds were confirmed by other methods. The Cys 7-Cys 161
disulfide bond is evidenced by the presence of co-eluting
peptides S39 a and b, T40 a and b, and K66 a and b. Further
evidence, as shown in Figure 9.B-5, is the separation of
reduced K66 a and b on the same chromatographic system as
the original peptide maps. The presence of Cys 29-Cys 33
was confirmed by amino acid composition of tryptic peptide
T44, in which the disulfide bond had been cleaved by
reduction and carboxymethylation.

The Ser and Asn residues linked to carbohydrate moieties are
not recovered from the sequencer, and therefore gaps at
these positions are expected. On this basis, and in
conformance to the consensus sequence for asparagine-linked
carbohydrate moieties Asn-x-Ser/Thr, Asn residues at 24, 38,
and 83 were identified as sites of oligosaccharide
attachment. A gap in the sequence is also present at Ser
126, indicating an O-linked carbohydrate moiety. The
presence of carbohydrate on Ser 126 is confirmed by the
amino acid composition of peptide S49, which indicated two
ser residues and galactosamine. A description of the N- and
O-linked carbohydrate moieties of r-HuEPO is presented in
Section 9.C.
The complete primary protein sequence analysis of r-HuEPO indicates that the amino acid sequence of this recombinant protein conforms to that deduced from the sequence of the coding DNA. The Arg 166, coded for by the erythropoietin gene (Section 2.B) appears to be cleaved post-translationally, resulting in a C-terminal residue of Asp 165. The detailed analysis of the C-terminus of erythropoietin is described later in this Section.

b. Sequence Analysis of u-HuEPO

The complete amino acid sequence of u-HuEPO has also been determined. Material purified by the method of Miyake et al., 1977 (provided by Dr. E. Goldwasser, University of Chicago) was used for this analysis.

Purified u-HuEPO was subjected to three separate and different protease digestions using TPCK-treated trypsin for two digests (the first in 10 mM CaCl₂, 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 fractionated by reversed phase HPLC immediately following digestion. Peptides were eluted by a gradient of trifluoroacetic acid (TFA) to acetonitrile/TFA.
Automated sequence analyses of intact proteins and peptide fragments were performed with a gas-phase sequenator as described above. PTH-cysteiny1 residues were identified as PTH-cysteic acid residues by reversed phase HPLC on a C18 column (Rainin) after oxidation of the Edman degradation product with performic acid at 0°C. In situ cyanogen bromide (CNBr) cleavage of the remainder of the protein molecule, following extensive sequence analysis of the intact protein, was performed using 70% CNBr in formic acid.

The complete amino acid sequence for the u-HuEPO is shown in Figure 9.8-6. Data obtained from sequencing the intact protein and CNBr fragments were used to establish the order of sequences of peptides obtained by proteolytic cleavage of u-HuEPO. All of the residues were assigned positions by sequencing except the asparagines at positions 24, 38, 83, which are the three N-linked glycosylation sites, and one cysteine at position 161.

These results demonstrate that the amino acid sequence of u-HuEPO and r-HuEPO are identical. With the exception of the Arg 166, both conform to the amino acid sequence deduced from the human erythropoietin gene.
3. Carboxy-Terminal Analysis

An arginine residue at position 166 is indicated by the erythropoietin gene sequence (Section 2.B). However, neither tryptic peptide T4a or endo lys-C protease peptide K66b reveal the presence of Arg 166; both peptides end with Asp 165. Several other analyses performed both at Amgen and at the Kirin Pharmaceutical Laboratory (Maebashi, Japan) were used to verify the C-terminus of r-HuEPO.

a. Carboxypeptidase P Digestion

Intact r-HuEPO in 0.05% Brij-35, pH 4.0 was treated with carboxypeptidase P (E:S = 1:50) at room temperature. Aliquots of the carboxypeptidase digest were collected at 0, 30, 60, 120, and 240 minutes and the reaction terminated with the addition of 10% TFA to each aliquot. The digest aliquots were analyzed on an amino acid analyzer to determine the residues removed. The results, as shown in Figure 9.B-7, indicate that Thr-Gly-Asp is the C-terminal sequence of r-HuEPO.

The same results were obtained with u-HuEPO.
b. Hydrazinolysis

Both r-HuEPO (prepared both by Amgen and by Kirin) and u-HuEPO (purified by antibody-affinity chromatography followed by reversed phase-HPLC) were heated at 80°C for five hours in anhydrous hydrazine (250 μg erythropoietin in 0.5 ml of anhydrous hydrazine) containing Amberlite CG60 (2.5 mg).

After removing hydrazides with benzaldehyde, the reaction mixture was analyzed on an amino acid analyzer. Only aspartic acid was detected as a free amino acid in approximately 40% yield, indicating that the C-terminal amino acid residues of both r-HuEPO and u-HuEPO are identical and are aspartic acid.

c. Lysyl Endopeptidase Digestion

r-HuEPO was digested with lysyl endopeptidase in 0.05 M ethylmorpholine buffer, pH 8.6, at 30°C for two hours (E:S = 1:200) and subsequently reduced with 2-mercaptoethanol at 37°C for one hour. The reaction mixture was fractionated by reversed phase HPLC (using a TFA to TFA/acetonitrile gradient. The C-terminal peptide fragment was isolated using chemically synthesized dodecapeptide (with arginine as the C-terminal amino acid residue) and undecapeptide (with aspartic acid as the C-terminal amino acid residue) as
marker peptides. The isolated peptide was subjected to automated Edman degradation and carboxypeptidase Y digestion. The results show that the C-terminal peptide of r-HuEPO consists of 11 amino acid residues with aspartic acid at the C-terminus.

The undecapeptide, but not the dodecapeptide, is present in the lysyl endopeptidase digest of u-HuEPO, indicating aspartic acid is the C-terminus.

d. Trypsin Digestion

r-HuEPO produced both by Amgen and by Kirin was digested with TPCK-treated trypsin in 0.2 M NaHCO₃, pH 8.0, at 37°C for one hour (E:S = 1:50) and the reaction mixture fractionated by reversed phase HPLC. The C-terminal tryptic peptide was isolated by using chemically synthesized tetrapeptide (with arginine as the C-terminal amino acid residue) and tripeptide (with aspartic acid as the C-terminal amino acid residue) as marker peptides. A tripeptide having a sequence corresponding to the C-terminal Thr-Gly-Asp was isolated and identified but no tetrapeptide corresponding to Thr-Gly-Asp-Arg was detected, indicating aspartic acid is the C-terminal amino acid.
The tripeptide, Thr-Gly-Asp, was present in the tryptic digest of r-HuEPO.

e. RNA Sequencing

The nature of the processing of the C-terminal Arginine has been studied at the nucleic acid level. The codon for the C-terminal Arginine has been checked by DNA sequence analysis multiple times and has been independently confirmed (Jacobs, et al., 1985). In order to confirm that the r-HuEPO gene mRNA transcripts from the production cell line (MWC 51B) code for the C-terminal Arginine poly A+ RNA isolated from MWC 51B cells was directly sequenced.

A synthetic oligomeric primer (5'GTTGGTGAGGGAGGTGGG 3') was used to prime the chain extension from a site 24 nucleotides 3' of the terminator codon and to direct the sequence determination toward the r-HuEPO coding sequence. The sequencing procedure is a modification of the Sanger dideoxy method using reverse transcriptase to copy the mRNA and dideoxy-analogs to terminate the chain extension reactions at specific nucleotides (Zimmerman and Kaesberg, 1978). 160 bases were determined using this approach. This covered the region from the 3'-end of the primer through the terminator codon and extending an additional 46 codons into
the r-HuEPO coding sequence. The amino acid sequence translated from the mRNA sequence exactly matches the r-HuEPO and u-HuEPO C-terminal peptide sequence with the exception of the C-terminal Arginine codon. The mRNA sequence clearly indicated that the final codon is an Arginine. The results of these experiments confirm that the C-terminal Arginine is coded by the r-HuEPO gene and no mutations have been introduced. It is concluded that the C-terminal Arginine is incorporated during translation and then removed post-translationally.

f. Processing Studies

In a study of C-terminal sequence analysis of r-HuEPO harvested early in the cell culture production cycle, Asp 165 was found to be the C-terminal amino acid on day one (the earliest time sampled) after initiation of serum-free production. In this study, r-HuEPO purified from serum-free medium was subjected to C-terminal sequence analysis using carboxypeptidase P. The results clearly indicate that Arg 166 is processed within the first 24 hours of production in cell culture.

Although the results presented in this Section suggest processing of the residue 166 of both r-HuEPO and u-HuEPO,
the mechanism of processing is not known. Processing may take place intracellularly or after secretion into the cell culture medium. In support of the latter hypothesis, a carboxypeptidase B-like activity of about 0.03 μmole/mg protein/hr was found in concentrated diafiltered medium using Bγ-Gly-Arg or a synthetic erythropoietin C-terminal peptide as substrate. Similar activity, 0.04 μmole/mg protein/hr was also found in concentrated human urine. The amount of activity detected is sufficient to quantitatively process all of the r-HuEPO present in the concentrated diafiltered medium. The carboxypeptidase B-like activity was not found in the r-HuEPO fraction following the first chromatographic step, anion exchange chromatography (Section 3.0.2), or in purified bulk r-HuEPO. While these results do not prove that this is the actual mechanism of removal of the C-terminal arginine of r-HuEPO, they demonstrate that extracellular processing is possible.
4. Amino Acid Composition

The amino acid composition of r-HuEPO is determined by acid hydrolysis (constant boiling HCl) of the protein at 110°C for 24 hours followed by separation of amino acids by ion exchange chromatography using a suitable amino acid analyzer. The amino acids analyzed are quantified by comparison to a standard mixture of amino acids of known concentrations which are quantified in the same way. The results of amino acid composition analysis for a typical purified bulk product preparation of r-HuEPO are shown in Figure 9.8-8. The theoretical composition of r-HuEPO reflects the C-terminal analysis determination that r-HuEPO contains only 165 amino acids, and that the C-terminal Arg 166 deduced from the gene sequence is not present in the mature protein. The data indicate that the sample is a highly purified protein with an amino acid composition consistent with r-HuEPO.

Since cysteine and cystine residues are not determined during the standard amino acid analysis due to destruction during HCl hydrolysis, an additional experiment was performed to quantitate these residues. Intact r-HuEPO was treated with performic acid to oxidize the cysteines to cysteic acid. The cysteic acid residues, which are more stable during HCl hydrolysis, were determined by the method previously described. The results (presented in Figure 9.8-9) are consistent with the theoretical value of four cysteines residues.
5. Hydrodynamic Studies of r-HuEPO

In collaboration with Dr. D. Yphantis, University of Connecticut, sedimentation equilibrium experiments were performed using the analytical ultracentrifuge to determine the molecular weight of r-HuEPO.

The partial specific volume of r-HuEPO in 20 mM sodium citrate, 100 mM NaCl, pH 7.0 was determined using the Anton Parr DMA-02C precision density meter (Lee et al., 1979). Four independent measurements gave a value of 0.698 ± 0.004 ml/g with no concentration dependence within experimental error. This value is significantly lower than the value of 0.720 ml/g calculated for the protein moiety only, reflecting the glycosylation of r-HuEPO.

Sedimentation equilibrium experiments were performed using a Beckman Model E ultracentrifuge equipped with a pulsed argon ion laser, a digital laser controller (Yphantis et al., 1984), and an automated control system for photography. External loading cells with three pairs of channels were used at speeds of 22,000, 30,000 and 40,000 rpm. Loading concentrations were 0.09, 0.23, and 0.62 mg/ml. Data analyses were performed using the non-linear least squares approach (Johnson et al., 1981) with various assumed models. No significant dependence of the
apparent molecular weight on either speed or loading concentration was observed. Also, the apparent constancy of the Z-average molecular weights calculated from the data at varying speeds and loading concentrations indicate no substantial non-ideality under the experimental conditions. Joint fitting of the data from several speeds and loadings resulted in a best estimate of the molecular weight of r-HuEPO of 30,400 ± 400 g/mole. Since the sequence molecular weight of the protein moiety is 18,244 g/mole, the weight fraction of carbohydrate for this glycoprotein is estimated to be 0.40.

The possibility of the presence of more than one component was addressed by using the combination of the sensitivity of least-squares fitting procedures, the precision of the interference optical system, and the fractionation in the centrifugal field to detect the presence of larger and smaller species (Davis et al., 1987). No components other than r-HuEPO were observed. The experimental conditions set upper limits of 0.005 for the weight fraction of any component with a molecular weight twice or more the molecular weight of the main component and of 0.01 for the weight fraction of any component one half to one quarter the size of r-HuEPO, assuming similar buoyancy factors for all species. It was not possible to set useful limits for the
amounts of species nearly the same size as the principal
species, such as would result from the heterogeneity of the
carbohydrate moiety.

The apparent molecular weight of u-HuEPO has been the subject of
several reports. Determinations based on gel filtration under
non-denaturing conditions or gel electrophoresis in the presence
of SDS are not reliable, as the former method is a function of
the Stoke's radius and not the molecular weight of a protein,
and the latter method is confounded by the anomalous SDS binding
characteristics of glycoproteins. At least three different
methods with sound theoretical foundations have been used to
determine the molecular weight of u-HuEPO in crude mixtures.
Radiation inactivation analysis (Rosse et al., 1963), analysis
by combined gel filtration and sucrose density
ultracentrifugation (O'Sullivan et al., 1970), and gel
filtration in 6 M guanidine hydrochloride (Shelton et al., 1975)
resulted in molecular weight estimates of 27,000, 32,600, and
33,000 g/mole, respectively. Given the diversity of the test
methods and assumptions involved in each, the molecular weight
determinations of u-HuEPO are in good agreement with the value
of 30,400 ± 400 g/mole obtained for r-HuEPO by analytical
ultracentrifugation.
From the molecular weight of r-HuEPO and its partial specific volume, the radius of the r-HuEPO molecule was calculated to be 20.2 Å using a spherical approximation. Comparison of this with the experimental Stokes radius of 32 Å, obtained from gel filtration (Figure 9.8-10) suggests two possibilities: r-HuEPO either is highly asymmetric or has an expanded structure. Both factors can cause a larger hydrodynamic effective volume and, hence, Stokes radius, as compared with a globular protein of the same molecular weight. An expanded structure could result from the three asparagine-linked and one serine-linked oligosaccharides found in r-HuEPO. Taking a spherical approximation for the protein moiety of r-HuEPO, the radius was calculated to be 17.5 Å. The difference between the experimental and calculated Stokes radius (14.5 Å) may be ascribed to the carbohydrate moieties. Each chain carrying several sugar residues in one direction might extend into solvent and hence significantly increase the Stokes radius. In support of this is the observation that a free disaccharide molecule has a hydrodynamic effective radius of 4-6 Å (Schachman and Lauffer, 1949; Laurent and Killander, 1964; Arakawa and Timasheff, 1982).
Carbohydrate Composition of r-HuEPO

The carbohydrate composition of several lots of r-HuEPO was determined as described in the text. Neutral and amino sugars were analyzed by gas chromatography and sialic acid by the resorcinol method. The results are expressed as mole of monosaccharide per mole of r-HuEPO. Theoretical values were calculated from the structures and populations of the N-linked and O-linked carbohydrate moieties shown in Figures 9.C-9 and 9.C-3 respectively.
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<th>Mannose</th>
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Theoretical Composition: O-linked 2.0, D-linked 1.6

Total: 13.2% O-linked, 9.0% D-linked, 0.0% Total.