EXHIBIT N-2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: **LIN, Fu-Kuen** Serial No.: 07/113,179 Filed: October 23, 1987 For: "PRODUCTION OF ERYTHROPOIETIN" Group Art Unit: 1805 Examiner: Examiner Hodges	I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C., 20231, on this date: January 3, 1994 Michael F. Borun (Reg. No. 25,447) Attorney for Applicant

APPLICANT'S AMENDMENT AND RESPONSE
UNDER 37 C.F.R. §§1.115 AND 1.111

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Dear Sir:

This is in response to the Office Action dated September 1, 1993 in the above-identified application wherein all previously allowed claims (65-69) were rejected under 35 U.S.C. §101 and 112, first and second paragraphs. Reconsideration and withdrawal of the rejections is respectfully requested in view of the following amendments and remarks.

AMENDMENTS

IN THE SPECIFICATION

At page 34, line 32, after "83" please insert --deposited with the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Md., under deposit accession No. A.T.C.C. 67545 on October 20, 1987--.

At page 42, line 24, after "λh E1]" please insert --, deposited with the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Md., under deposit accession No. A.T.C.C. 40381 on October 20, 1987--.

IN THE CLAIMS

Please cancel claims 65-69 without prejudice to Applicant's right to present claims of the same or similar scope in a duly-filed continuing application.

Please enter new claims 70 through 75.

--70. A process for the preparation of an *in vivo* biologically active glycosylated erythropoietin polypeptide comprising the steps of:

(a) growing,under suitable nutrient conditions, mammalian host cells transformed or transfected with an isolated DNA sequence encoding human erythropoietin; and

(b) isolating said glycosylated erythropoietin polypeptide therefrom.--

--71. A process for the preparation of an *in vivo* biologically active glycosylated erythropoietin polypeptide comprising the steps of:

(a) growing, under suitable nutrient conditions, mammalian host cells transformed or transfected with an isolated DNA sequence selected from the group consisting of (1) the DNA sequences set out in FIGS 5 and 6 or their complementary strands, (2) the protein coding sequences set out in FIGS 5 and 6 or their complementary strands, and (3) DNA sequences which hybridize under stringent conditions to the DNA sequences defined in (1) and (2); and

(b) isolating said glycosylated erythropoietin polypeptide therefrom.--

--72. The process according to claim 70 or 71 wherein said host cells are CHO cells.--

--73. The process according to claim 70 or 71 wherein said host cells are COS cells.--

--74. The process according to claim 70 or 71 wherein said DNA is cDNA.--

--75. The process according to claim 70 or 71 wherein said DNA is genomic DNA.--

REMARKS

Applicant acknowledges with thanks the courtesy of an interview granted by Examiners Hodges and Schwartz to the undersigned counsel, Mr. Odre and Mr. Watt on November 18, 1993. As reflected in the Interview Summary Record (Paper No. 30), agreement was not reached on patentability of the pending claims, but the Examiner agreed to consider claim amendments which Applicant believes will moot the outstanding Section 112 rejections as well as arguments which Applicant believes will overcome the outstanding Section 101 rejection with respect to the subject matter claimed.

The above-requested amendments to the specification correspond to amendments which are the subject of a Certificate of Correction in U.S. 4,703,008 and do not constitute new matter. A copy of the Certificate is attached as Exhibit 1 hereto.

Upon entry of the above-requested amendments to the claims, prior allowed claims 65-69 will be withdrawn and replaced by new claims 70 through 75. As addressed in detail below, new independent claims 70 and 71 address preparative processes respectively involving erythropoietin DNAs which correspond to the DNAs of claims 2 and 1 of U.S. 4,703,008. Multiple dependent claims 72-75 correspond to prior claims 66-69.

I. The Outstanding Rejections

Prior allowed claims 65-69 were newly rejected under 35 U.S.C. §101 upon the assertion that "patentable utility" was lacking for the process as it might be applied to the preparation of glycosylated polypeptides other than erythropoietin.

Claims 65-69 were newly rejected upon the allegation that the invention thereof "is not patentably distinct from claim 9 of commonly assigned U.S. Patent No. 4,667,016 (Lai *et al.*)."

Claims 65-69 were newly rejected under the judicially created doctrine of obviousness-type double patenting in view of claim 9 of U.S. Patent 4,667,016.

Claims 65-69 were newly rejected under 35 U.S.C. §112, first paragraph as allegedly non-enabled with respect to the claim 65 recitation of a mammalian host cell "capable of effecting post-translational glycosylation of polypeptides expressed therein" and with respect to the recitations of claim 65 steps (i), (ii) and (iii). It was noted that the rejections could be overcome by deleting these recitations from the claims.

Claims 65-69 were newly rejected under 35 U.S.C. §112, first paragraph, as allegedly non-enabled except for claims limited to preparation of *human* erythropoietin.

Claims 65-69 were newly rejected under 35 U.S.C. §112, second paragraph, upon the allegation that references therein to "polypeptide" production and host cell glycosylation "capability" were indefinite.

II. Patentability Arguments

Applicant respectfully submits that the outstanding rejections of claims 65-69 under 35 U.S.C. §112, first and second paragraphs, were not properly made, but notes that they are mooted by present claims 70-75 which do not include the particular claim 65 recitations objected to as allegedly indefinite or non-enabled. Applicant also submits that no proper basis exists for rejection of prior claims 65-69 or new claims 70-76 under 35 U.S.C. §101 or 35 U.S.C. §103 based on the subject matter of claim 9 of Lai *et al.* U.S. 4,667,016.

A. The Section 101 and 112 Rejections Based On Claim Terminology and Support Therefor Are Not Properly Applied to Claims 70-75

As noted at the interview of November 18, 1993, Applicant respectfully disagrees with the Examiner's position that previously allowed claims 65-69 are appropriately subject to rejection under 35 U.S.C. §§101 and 112, but believes that amendments to the claims effectively moot the issues presented by the outstanding rejections.

1. The outstanding inoperability and indefiniteness rejections under Sections 101 and 112, second paragraph, addressing Applicant's reference in claim 65 to production of an "*in vivo* biologically active polypeptide" are not believed to be proper in view of the claim 65 recitation in part (a) to of use of "an isolated DNA sequence encoding human erythropoietin." Reference to such DNA constitutes a positive limitation of the claim and specifically characterizes the product obtainable through practice of the process. In any event, new claims 70 and 71 specifically refer to preparation *erythropoietin* polypeptides and thus no proper basis exists for maintaining either that the claimed subject matter lacks patentable utility under 35 U.S.C. §101 or is indefinitely recited under 35 U.S.C. §112, second paragraph.

2. The outstanding non-enablement and indefiniteness rejections under 35 U.S.C. §112, first and second paragraphs, addressing Applicant's reference in claim 65 to "a mammalian host cell which is capable of effecting post-translational glycosylation of polypeptides expressed therein" are respectfully traversed. Applicant has disclosed the production of *in vivo* biologically active erythropoietin in mammalian cells and has specifically exemplified the production of *in vivo* biologically active monkey and human species erythropoietin in monkey (COS) and Chinese Hamster Ovary (CHO) cells. Numerous other mammalian cells capable of effecting glycosylation of expressed polypeptides were known to those skilled in the art at the time of the present invention. In any event, the terminology objected to by the Examiner does not appear in new independent claims 70 and 71 and the outstanding rejection is therefore mooted.

3. The outstanding rejection of claims 65-69 as non-enabled under the first paragraph of Section 112 with respect to recitations (i), (ii) and (iii) of claim 65 is also respectfully traversed. The Examiner's position that these transcription, translation and glycosylation steps have no basis in the specification is at odds with the Examiner's collateral concessions that production of glycosylated proteins is enabled by the specification and that these steps are "inherent in the production of a glycosylated polypeptide." (See Action of September 1, 1993 at page 8.) In any event, because independent claims 70 and 71 do not include specific recitation of these steps, the basis for rejection is mooted.

4. The Section 112, first paragraph, rejection of prior claims 65-69 on grounds that the specification enables only *human* erythropoietin production is respectfully traversed. Applicant has fully disclosed and enabled DNA/DNA hybridization procedures for the isolation of a human species genomic erythropoietin clone as set out in Figure 6, a monkey species cDNA clone as set forth in Figure 5 and a human species erythropoietin cDNA clone (isolated *via* reverse transcription of mRNA produced in human erythropoietin-producing COS cells transfected with human genomic DNA.) In addition, Applicant has disclosed DNAs encoding specific analogs of erythropoietin. See specification page 91, lines 5 to 92, line 2.

The issue of support for erythropoietin encoding DNAs for species other than *human* species is mooted in the context of new claim 70 which recites the use of DNA encoding *human* erythropoietin. This recitation is derived from claim 2 of U.S. 4,703,008. New claim 71 recites use of a DNA substantially as set out in claim 1 of U.S. 4,703,008 and, as such, is not limited to use of a DNA encoding a human species erythropoietin polypeptide. Applicant submits that the scope of the DNA recitation in claim 71 is fully enabled by the present specification. Human species genomic and cDNA sequences as well as monkey species cDNA were isolated as a result of the use of DNA/DNA hybridizations involving protein coding DNAs corresponding to the protein coding sequences of Figures 5 and 6. *In vivo* biologically active human and monkey species glycoproteins were produced in mammalian cells in full support of the recitations of new claim 71. Applicant thus submits that all requirements of the first

paragraph of Section 112 have been met for claims 70-76 and rejection on grounds of non-enablement would not be proper.

B. Obviousness and Obviousness-Type Double Patenting Considerations Do Not Apply To The Present Claims

Applicant notes at the outset that the erythropoietin purification processes of Lai *et al.* U.S. 4,667,016 are not available as prior art under 35 U.S.C. §103 with respect to the presently claimed erythropoietin processes. The present application is entitled to priority of the December 13, 1983 filing date of U.S. patent application Serial No. 561,024. (See, e.g., declaration of Interference issued as Paper No. 21 herein.) The Lai *et al.* patent is based on U.S. patent application Serial No. 747,119 filed June 20, 1985, over nineteen months later. Thus no proper rejection of the present claims under Section 103 can be premised on the disclosures of the Lai *et al.* patent.

Applicant further respectfully submits that no proper basis exists for a holding of obviousness-type double patenting for the claimed subject matters *vis-a-vis* the subject matter of claim 9 of the Lai *et al.* patent.

An appropriate starting point for consideration of the obviousness-type double patenting issue is the recent Federal Circuit decisional authority of *In re Braat*, 937 F.2d 589 (Fed. Cir. 1991) and *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272 (Fed. Cir. 1992). At pages 592-593 of the *Braat* decision, Judge Rich set out the general basis for the judicially created doctrine, noting that the obviousness/non-obviousness determination is based on analysis of the claims, rather than the disclosures of the specification supporting those claims.

> Obviousness-type double patenting is a judicially created doctrine intended to prevent *improper* timewise extension of the patent right by prohibiting the issuance of claims in a second patent which are not "patentably distinct" from the claims of a first patent. *See in re Longi*, 759 F.2d 887, 892, 225 USPQ 645, 648 (Fed.Cir. 1985). The doctrine has also been phrased as prohibiting claims in the second patent which define "merely an obvious variation" of an invention claimed in the first patent. *In re Vogel*, 422 F.2d 438, 441, 164 USPQ 619, 622 (CCPA 1970). We note at the

> outset the difficulty which arises in all obviousness-type double patenting cases of determining when a claim is or is not an obvious variation of another *claim*. As this court's predecessor, the CCPA, noted in *Vogel*, 422 F.2d at 441-42, 164 USPQ at 622, a claim often does not describe any particular thing but instead defines the boundary of patent protection, and it is difficult to try to determine what is a mere obvious variation of a legal boundary. However, this court has endorsed an obviousness determination similar to, but not necessarily the same as, that undertaken under 35 USC § 103 in determining the propriety of a rejection for double patenting. *See Longi*, 759 F.2d at 892 n. 4, 225 USPQ at 648 n. 4.

The decision went on to premise reversal of the Board's holding of double patenting upon the Board's failure to support its holding by a "two-way" determination of obviousness, for the claimed subject matter starting:

> ...The Board erred in sustaining the double patenting rejection without making such a 'two-way' determination.

As part of its holding in *Braat*, the Federal Circuit noted at pages 594-595 that only an "unjustified" timewise extension of parent protection would support an obviousness-type double patenting rejection.

The Federal Circuit decision in *General Foods* addressed the issue of double patenting in the context of a first patent's claims directed to a process for decaffeination of coffee through water-moist CO_2 treatment to remove caffein and a second patent's claims to caffein purification involving multiple steps applied to the water-moist CO_2 fraction containing caffein such as developed during the decaffeination process of the first patent. In the Federal Circuit's analysis supporting reversal of the District Court holding of double patenting, the court held at pages 1278-1279 that:

> Double patenting is altogether a matter of what is claimed. Claim interpretation is a question of law which we review de novo. *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 228 USPQ 90 (Fed.Cir. 1985). As we construe the claims here involved, claims 1 and 4 of the patent in suit, '639, define a process of decaffeinating raw coffee with supercritical water-moist carbon dioxide and recovering the decaffeinated coffee. They say nothing about what happens to the caffeine. Claim 1 of the '619 patent, relied on to show double patenting, defines a *9-step process* of "obtaining caffein from green coffee." Anything less than a process with all 9 steps is not what is claimed, and is, therefore, not patented. Claims must be read as a whole in analyzing a claim

> of double patenting. *Carman Indus., Inc. v. Wahl*, 724 F.2d 932, 940, 220 USPQ 481, 487 (Fed.Cir. 1983) ("we wish to clarify that double patenting is determined by analysis of the claims as a whole.") These two inventions, decaffeination of coffee and recovery of caffeine, are separate, *patentably distinct* invention between which there cannot be double patenting. Clearly the two patents do not claim the *same* invention, and this is not argued. Under an obviousness-type double patenting analysis, neither *claimed* process is a mere obvious variation of the other. No other kind of "double patenting" is recognized, so there is no double patenting. That concludes the case so far as this appeal is concerned.

In the discussion of legal authorities supporting its decision in *General Foods*, the Federal Circuit addressed the decisions of the Court of Customs and Patent Appeals in *In re Vogel*, 422 F.2d 438 (CCPA 1970) and *In re Borah*, 354 F.2d 1009 (CCPA 1966). First addressing *Vogel*, the Court reiterated the decision's restatement of the law of double patenting at page 1278 as follows:

> To summarize it, the opinion says that the first question is: Is the same invention being claimed twice? If the answer to that is no, a second question must be asked: Does any claim in the invention define merely an obvious variation of an invention claimed in the parent asserted as supporting double patenting? If the answer to that question is no, there is no double patenting.

At page 1278-1279 of the *General Foods* decision, the Court maintained that the *Borah* decision

> ...shows beyond question that the determining factor in deciding whether or not there is double patenting is the existence vel non of *patentable difference* between two sets of claims. The phrases actually used in the opinion include 'patentably distinguishable.' 'patentable distinctions,' and 'whether such differences would have been obvious to one of ordinary skill in the art. They are all equivalent.

Furthermore, Applicant submits that the present erythropoietin production process claims (as represented by claims 70 and 71) and the cited erythropoietin purification process claim 9 of the Lai *et al.* patent recite inventions which are patentably distinct from each other and that issuance of the claims pending in the present application would provide no extension whenever of the protection of the Lai *et al.* claims, much less an unjustifiable extension thereof.

Present claims 70 and 71 recite:

> 70. A process for the preparation of an *in vivo* biologically active glycosylated erythropoietin polypeptide comprising the steps of:
> (a) growing,under suitable nutrient conditions, mammalian host cells transformed or transfected with an isolated DNA sequence encoding human erythropoietin; and
> (b) isolating said glycosylated erythropoietin polypeptide therefrom.

> 71. A process for the preparation of an *in vivo* biologically active glycosylated erythropoietin polypeptide comprising the steps of:
> (a) growing, under suitable nutrient conditions, mammalian host cells transformed or transfected with an isolated DNA sequence selected from the group consisting of (1) the DNA sequences set out in FIGS 5 and 6 or their complementary strands, (2) the protein coding sequences set out in FIGS 5 and 6 or their complementary strands, and (3) DNA sequences which hybridize under stringent conditions to the DNA sequences defined in (1) and (2); and
> (b) isolating glycosylated erythropoietin polypeptide therefrom.

Claim 9 of the Lai *et al.* patent is in dependent form and recites:

> 9. The process of claim 8 applied to recovery of recombinant erythropoietin from a cell culture derived fluid.

In turn, independent claim 8 of the Lai *et al.* recites seven specific process steps applied in sequence:

> 8. A process for the efficient recovery of erythropoietin from a fluid, said process comprising the following steps in sequence:
> (1) subjecting the fluid to ion exchange chromatographic separation at about pH 7.0, thereby to selectively bind erythropoietin in said sample to a cationic resin;
> (2) stabilizing materials bound to said resin against degradation by acid activated proteases;
> (3) selectively eluting bound contaminant materials having a pKa greater than that of erythropoietin by treatment with aqueous acid at a pH of from about 4.0 to 6.0;
> (4) selectively eluting erythropoietin by treatment with an aqueous salt at a pH of about 7.0;
> (5) subjecting eluted, erythropoietin-containing fluids to reverse phase liquid chromatographic separation involving an immobilized C_4 or C_6 resin, thereby to selectively bind erythropoietin in said fluid to said resin;
> (6) selectively eluting bound erythropoietin from said resin with an aqueous ethanol solution of from 50 to 80 percent at a pH of from about 4.5 to about 8.0; and,

(7) isolating erythropoietin-containing fractions of the eluent.

Applying the first step of the *Vogel* two-step inquiry process reiterated in *General Foods*, the claims in issue clearly do not define the same invention "being claimed twice." The second inquiry, into whether claims 70 and 71 merely define an obvious variation of the invention of claim 9 of the Lai *et al.* patent, generates a similarly negative answer even ignoring the unavailability of the Lai *et al.* patent as a reference. Nothing claimed in claim 9 of the Lai *et al.* patent operates to render obvious the Applicant's methods for preparing *in vivo* biologically active glycosylated erythropoietin polypeptides. As the Examiner himself has noted at page 10 of the September 1, 1993 Office Action. "For example, at the time the invention was made, it was highly unpredictable that a heterologous protein would be produced in a biologically active glycoslated form." As previously maintained by Applicant, his production of *in vivo* biologically active glycoslated erythropoietin was among the first, if not *the* first, demonstrations of production of a biologically active obligate human glycoprotein, i.e., a human protein requiring glycoslation for *in vivo* biological activity. Lai *et al.* claim 9 is silent on the issue of glycosylation and *in vivo* biological activity. Because the Lai *et al.* claim to practice of seven recited purification steps on a recombinant source erythropoietin does not render obvious the "patentably distinguishable" processes claimed by claims 70 and 71 leading to biologically active erythropoietin polypeptides, no obviousness-type double patenting would exist upon issuance of the pending claims. The invention of claims 70 and 71 is simply *not* an obvious variation of the subject matter of Lai *et al.* claim 9.

Applicant further submits that, while not specifically called for by the *Vogel/General Foods* restatement, analysis of the claims in issue also reveals that the purification process subject matter of Lai *et al.* claim 9 is not an obvious variation of the erythropoietin production processes of claims 70 and 71. Nothing in the recitations of claims 70 and 71 operates to render obvious the sequential application of the seven purification steps of Lai *et al.* claim 9. As was the case with the subject matter considered in *General Foods*, the claim 70 and 71 process for producing biologically active erythropoietin products (like the claims to

decaffeinating coffee by water-moist CO_2 extraction of caffein) is silent concerning further processing by any means, much less the specific procedural means recited in the Lai *et al.* claim. Because the seven step purification process of Lai *et al.* claim is *not* simply an obvious variation of the subject matter of claims 70 and 71, no basis for a holding of obviousness-type double patenting exists.

Applicant has thus demonstrated two-way *non-obviousness* concerning the subject matter of the present claims and claim 9 of the Lai *et al.* patent.[1] As noted during the interview of November 18, the Lai *et al.* patent claims could not and did not provide protection to Applicant against the "mere" foreign practice of the processes of present claims 70 and 71. No basis for a bar to importation of a product concededly produced by a production process of present claims 70 and 71 could have been supported in the absence of additional proof that all seven purification process steps of Lai *et al.* claim 9 have been practiced to generate the imported products. Likewise, issuance of claims 70 and 71 would not provide a basis for "extension" of protection of Lai *et al.* patent claim 9 beyond the term of that patent.

Applicant's above-noted demonstrations of two-way non-obviousness and lack of any timewise "extension" of patent protection are believed to establish that no proper basis exists for application of the judicially-created doctrine of double patenting.

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[1] Compare *Braat, supra*, wherein it was held that a two-way *obviousness* demonstration was a requisite for a double patenting holding.

CONCLUSION

The foregoing amendments and remarks are believed to establish that claims 70-75 are in condition for allowance and an early notice thereof is solicited.

Respectfully submitted,

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