EXHIBIT 7

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	"Production of
FU-KUEN LIN	Erythropoietin"
Serial No: 113,179	Group Art Unit 127
Filed: October 23, 1987	Examiner (Expected): A. Tanenholtz
(Based on S.N. 675,298, filed November 30, 1984, issued as U.S. 4,703,008 on October 27, 1987)	

APPLICANT'S SECOND PRELIMINARY AMENDMENT

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

Sir:

Consistent with the February 18, 1988 favorable Decision On Petition To Make Special and the provisions of M.P.E.P. §708.02, please amend the above-identified application as follows:

IN THE SPECIFICATION

Please delete the entire text of page 1, lines 3-6 as amended October 23, 1987 and insert the following text in place thereof:

--This is a continuation of my co-pending U.S. Patent Application Serial No. 675,298, filed November 30, 1984 and issued as U.S. Letters Patent No. 4,703,008 on October 27, 1987, which was a continuation-in-part of my co-pending U.S. Patent Application Serial No. 561,024, filed December 13, 1983, now abandoned, and a continuation-in-part of Serial No. 582,185, filed February 21, 1984, now aban-

doned, and a continuation-in-part of Serial No. 655,841, filed September 28, 1984.--

Page 7, line 27, "32 member" should be --32-member--.

Page 8, line 22, please delete the second occurrence of "the".

Page 11, line 3, "Expt.Hematol." should be --Exp.Hematol.--.

Page 11, line 4, "(1980:" should be --(1980);--.

Page 11, line 6, please insert a space before "1832".

Page 13, line 13, please insert --"-- after "effects".

Page 13, lines 20-21, please insert --)-- after "propagation".

Page 22, line 4, "Tables V and VI" should be --Figures 5 and 6--.

Page 22, line 22, "Table VI" should be --Figure 6--.

Page 27, line 24, "Example" should be --Examples--.

Page 32, line 35, please delete the comma (,) after "Springs".

Page 48, line 15, please delete "glutamine" and insert in place thereof --glutamic acid--.

Page 48, line 29, "Table VI" should be --Figure 6--.

Page 54, line 36, "EcoR1" should be --EcoRI--.

Page 55, line 13, "BamH1" should be --BamHI--.

Page 55, line 15, "BamH1" should be --BamHI--.

Page 61, line 25, "hemogeneous" should be --homogeneous--.

Page 88, line 36, "lablled" should be --labelled--.

Page 91, line 29, please delete "a".

Page 92, line 10, "Table VI" should be --Figure 6--.

Page 95, line 10, "membrances" should be --membranes--.

IN THE CLAIMS

Please cancel claims 61-64 without prejudice to Applicant to pursue claims of the same or similar scope in a duly-filed continuing application.

Please enter new claims 65-69.

--65. A process for the preparation of an in vivo biologically active glycosylated polypeptide comprising the steps of:

(a) growing a mammalian host cell which is capable of effecting post-translational glycosylation of polypeptides expressed therein and which is transformed or transfected with an isolated DNA sequence encoding ~~a polypeptide having a primary structural conformation sufficiently duplicative of that of naturally occurring~~ human erythropoietin ~~to allow possession of the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, or the~~ progeny thereof, under nutrient conditions suitable to allow, in sequence,

(i) transcription within said host cell of said DNA to mRNA in the sequence of transcription reactions directed by the nucleotide sequence of said DNA;

(ii) translation within said host cell of said mRNA to a polypeptide in the sequence of translation reactions directed by the nucleotide sequence of said transcribed mRNA;

(iii) glycosylation within said host cell of said polypeptide in a pattern directed by the amino acid sequence of said translated polypeptide and sufficiently duplicative of the pattern of glycosylation of naturally occurring human erythropoietin to allow possession by the translated glycosylated polypeptide product of the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells; and

(b) isolating the glycosylated polypeptide so produced.

66. The process according to claim 65 wherein said host cell is a CHO cell.

67. The process according to claim 65 wherein said host cell is a COS cell.

68. The process according to claim 65 wherein said DNA is cDNA.

69. The process according to claim 65 wherein said DNA is genomic DNA.--

REMARKS

A. Amendments To The Specification

The above-requested amendments to the specification combine with those requested in Applicant's Preliminary Amendment dated October 23, 1987 to eliminate all typographical errors present in the specification as filed.

B. Reference To Related Applications

The present application is a continuation of U.S. Patent Application Serial No. 675,298, filed November 30, 1984 (as a continuation-in-part of Serial No. 655,841, filed September 28, 1984, and Serial No. 582, 185, filed February 21, 1984, now abandoned, and Serial No. 561,024, filed December 13, 1983, now abandoned). Application Serial No. 675,298 issued on October 27, 1987 as U.S. Letters Patent No. 4,703,008 (hereinafter "the '008 Patent"), with claims relating to novel erythropoietin DNA sequences. To facilitate consideration of the claims presented herein, Applicant attaches as Exhibit "A" hereto a copy of columns 39 to 42 of the '008 Patent which includes the 31 issued claims.

C. The Presently Claimed Subject Matter

Without prejudice to Applicant's right to pursue such further process claims as are supported by the disclosures of the present specification, Applicant has

submitted new claims 65-69 herein to that aspect of his invention which relates to novel methods for the production in mammalian host cells of human erythropoietin glycoprotein -- the first article of human manufacture ever to possess both the amino acid sequence and glycosylation needed for in vivo erythropoietin biological activity. As set out in detail hereafter, the practice in late 1983 of processes herein claimed is believed to constitute one of the first instances (if not the first instance) of the recombinant production of an in vivo biologically active obligate human glycoprotein, an event which has in turn allowed, for the first time, the provision of a human erythropoietin product in quantities necessary for human hematopoietic therapy.

Briefly summarized, independent claim 65 relates to a novel series of process steps wherein a mammalian host cell[1] capable of glycosylating the expressed polypeptides is first transformed or transfected with a DNA sequence[2] encoding a specifically delineated polypeptide, i.e., one having sufficient amino acid sequence homology to natural human erythropoietin to allow it to qualify, amino acid sequence-wise, for potential in vivo biological activity. (The DNA reagent employed in the transformation/transfection process is itself the novel and unobvious subject matter of '008 Patent claim 7 and the resulting host cells are as recited in claim 24 of the Patent.) The claim 65 process calls for host cell growth in culture under conditions

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1 Including such non-human, non-kidney cells as COS and CHO cells as specified in claims 66 and 67.

2 Including, e.g., cDNA and genomic DNA as specified in claims 68 and 69.

wherein transcription, translation and glycosylation processing occurs. More particularly, the claim calls for mRNA transcript formation according to the per se unique directions provided by the recited DNA sequence. (Illustratively, the formation of a full length coding region transcript of erythropoietin cDNA ordinarily involves no less than 582 specifically ordered nucleotide additions for the formation of the mRNA polymer.) Also delineated by claim 65 is performance of a specific sequence of translational events giving rise to polypeptide formation. (Again, a minimum of 193 specific alignments of tRNA's to the mRNA and 192 peptide bond formations are involved to link, in order, the amino acids constituting the full length primary structural conformation.) Further required by claim 65 is the glycosylation processing of the translated polypeptide at sites directed by the order of amino acids of the translated polypeptide so that the resulting product, upon isolation, will have the pattern of glycosylation which is also required for in vivo biological activity.

D. The Examiner's Position Regarding Method Method Claims During '008 Patent Prosecution

In the course of prosecution of Application Serial No. 675,298 leading up to issuance of the '008 Patent, certain erythropoietin production method claims (later withdrawn without prejudice) were objected to by Examiner Tanenholtz (one of three Examiners handling the application) on the following grounds:

> Claims 69-72 are rejected under 35 U.S.C. 103 as being unpatentable over Talmadge et al and who disclose the basic process of recombinantly expressing and isolating polypeptides as claimed herein. Even where it is considered that one more of the starting

> materials is novel, the application of an old process to such materials to produce the expected result would still be obvious within the meaning of 35 U.S.C. 103; In re Durden, supra; In re Larsen, 141 U.S.P.Q. 730 (1964). Whether or not a product produced by the claimed process possesses any unique or unexpected properties is not material to the question of whether or not the process itself would have been obvious." (Emphasis added)

Applicant respectfully submits that the above statements of the Examiner construing the decision of the Durden case were legally erroneous and that application of such constructions to the presently claimed subject matter would also constitute error.

E. Remarks In Support Of Patentability of the Claims

Applicant respectfully submits that the subject matter of claims 65-69 is clearly patentable and that no proper basis exists for rejection of the claims under 35 U.S.C. §103. In support of this position, Applicant provides the following series of remarks relating to: (1) the characteristics of human erythropoietin as an "obligate glycoprotein"; (2) the distinctness of the patentability issues herein from issues addressed in the decision in In re Durden; (3) the lack of relevance to patentability of prior art cited during prosecution of the '008 Patent; and (4) the lack of relevance to patentability of prior art recently ascertained and relating generally to recombinant production of glycoproteins.

1. The Characteristics of Erythropoietin As an Obligate Glycoprotein

"State of the art" knowledge with respect to erythropoietin at the time of the present invention revealed to the skilled worker that the in vivo biological activity

of this human glycoprotein was dependent not only on its specific amino acid sequence conformation, but also its array of glycosylation. Thus, Goldwasser et al., J.Biol.Chem., 249(18), 4302-4306 (1974) [Exhibit "B" hereto"] report at page 4302 that:

> Erythropoietin, a glycoprotein that induces normal erythrocyte development, has 16 to 18 sialic acid residues per mole. Desialation results in complete loss of biological activity when it is assayed in vivo. When the assay is done in vitro asialoerythropoietin has full activity, or when assayed at low levels of hormones is about three times more active than the native hormone. The loss of activity can be explained by the hepatic removal of asialo-glycoproteins from the circulation.

Goldwasser, Fed.Proc., 34(13), 2285-2292 (1975) [Exhibit "C" hereto] further reports at page 2288 that:

> The role of sialic acid in epo activity appeared for a time to be paradoxical since asialo epo has no activity when assayed by in vivo methods, but had full, or increased, activity when assayed [in vitro] by a marrow cell culture method. The explanation of this apparent paradox was derived from the studies of Morell et al. who showed that, in general, asialo glycoproteins were cleared from the circulation at a much greater rate than the native form. This rapid clearance was effected by hepatic cells that specifically interacted with the newly terminal galactose residues exposed by desialation. The liver system was shown to be a saturatable one, so that other asialoglycoproteins could occupy all of the binding sites and permit a nearly normal clearance rate for a particular test asialo glycoprotein. These authors also showed that, if the terminal galactose residues of asialo glycoproteins were oxidized or removed, the modified asialo glycoproteins would remain in the circulation for a nearly normal period.
>
> Lukowsky and Painter have shown that partially desialated epo, when oxidized with galactose oxidase, had its in vivo biological activity restored. In this laboratory, we have shown that completely desialated epo similarly treated had about 45% of the original in vivo activity. These data

> suggest that galactose is the penultimate carbohydrate residue but is not required for biological activity. In addition, asialo-orosomucoid and the tetrasaccharide stachyose could act as competitors in assay animals, permitting about 30% of the original (native) activity to be found in asialo epo. Lactose, on the other hand, does not act as a competitor, so the minimal size of oligosaccharide required must be either three or four.
>
> We have also found that asialo epo is more susceptible to tryptic digestion and heat inactivation than is the native form. The asialo hormone has about three times more activity, when assayed in vitro at the lower end of the dose-response curve (1-4 milliunits), than the native form. This may be due to greater ease of binding of asialo epo to the epo-responsive cell receptors when the negative charge on the hormone is reduced by desialation. (Citations omitted)

The skilled worker at the time of the present invention would thus have understood that if preparations of in vivo biologically active human erythropoietin were to be provided in therapeutic quantities by recombinant means, a method would have to be devised whereby (a) an appropriate array of glycosylation including sialic acid terminal residues and, possibly, penultimate galactose residues would be provided on (b) a polypeptide with requisite amino acid sequence homology to erythropoietin. Unlike other human glycoproteins such as the interferons and Interleukin-2, human erythropoietin was conspicuously known to be an obligate glycoprotein and no hope at all existed for isolating in vivo active material from recombinant host cells unless, at a minimum, both the issues of required polypeptide sequence and of required glycosylation could be successfully attended to.

2. Factual Distinctness of Patentability Issues herein from those of In re Durden

The decision of the C.A.F.C. in In re Durden, 226 USPQ 359-362 (1986) was noted by the Examiner as potentially relevant to patentability of claims originally presented in parent Serial No. 675,298. Applicant respectfully submits that the decision is not in any way controlling on the determination of nonobviousness of claims 65-69 under Section 103. This is so because the factual context which was the focus of the Court's deliberations in the Durden case is wholly distinct from that extant with respect to the invention claimed herein.

Here, as in Durden, method claims are in issue and practice of the claimed method involves use of patentable starting materials to obtain patentable products. It will be recalled at the outset, however, that the C.A.F.C. specifically declined to provide any "general rule" for application to all cases wherein the patentability of a method for manufacturing a novel product using a novel starting material is under consideration.

> We reiterate another principle followed in obviousness issue cases, which is to decide each case on the basis of its own particular fact situation. What we or our predecessors may have said in discussing different fact situations is not to be taken as having universal application.
>
> * * * * *
>
> We are sure that there are those who would like to have us state some clear general rule by which all cases of this nature could be decided. Some judges might be tempted to try it. But the question of obviousness under §103 arises in such an unpredictable variety of ways and in such different forms that it 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. The task may sometimes be easy and sometimes difficult; and as this case shows, not all of those required to decided may agree. But such is the way of the "law".

Against this background, only a cursory examination of the facts and stipulated issues in the Durden appeal is necessary to show that the final outcome in that case has no controlling effect here.

In Durden, the claim under consideration was directed to performing a well known chemical conversion of an oxime to a carbamate ester. More specifically, the claim called for use of a novel oxime-substituted, 6-membered ring compound as a starting material. The prior art showed successful carbamate ester formation using an oxime-substituted 5-membered, ring compound as the starting material. The Examiner properly noted two structural differences between applicant's and the prior art's starting materials and requested factual input from the applicant as to whether, in view of the success achieved in the prior art, the distinct features of the new starting material might have any influence on whether a skilled worker could reasonably expect the desired carbamate ester product to be formed. As noted by the C.A.F.C., no such facts concerning any potentially unexpected results of the process were provided to the Examiner or the Board.

Given this factual background, the concisely-stated legal issue decided by the C.A.F.C. in Durden was:

> ...whether a chemical process, otherwise obvious, is patentable because either or both the specific starting material employed and the product obtained, are novel and unobvious. (id at page 360, emphasis in text.)

The facts relevant to a determination of obviousness in the present case are completely different. The subject matter of the present claims conspicuously involves myriad biological processes rather than a single chemical process. As indicated earlier, even after the host cell's biological transformation or transfection has been achieved, there remain to be performed literally thousands of complex individual cellular reactions in a specific order directed first by the novel DNA sequence, then by the mRNA transcript of the DNA, and finally by the translated polypeptide sequence, all within the infinitely complex biochemical milieu of the host cell.

The issue presented here, therefore, is not that which was before the Durden Court: whether a concededly obvious process, providing its entirely expected result, can be bootstrapped to the stature of patentable subject matter merely by calling for its application to a new starting material or by causing it to be applied to formation of a new product. In such a case, the outcome of deliberation on potential patentability is invariably negative because, by definition, merely achieving the expected cannot be patentable.

The issue here presented is the threshold issue of whether the series of processes whose practice is called for by the claims is an obvious series of processes giving rise to an expected result. Deliberation on this issue must involve consideration of the novel nature of the DNA sequence employed in the process and also must involve consideration of whether the product isolated could reasonably have been expected to come into existence by practice of the recited procedures.

The Examiner's position in Serial No. 675,298 construes the Durden decision to indicate that the C.A.F.C. has relegated evidence regarding properties of a claimed process's product to the junk heap of immateriality for purposes of determining obviousness of the process. This is simply not true. While the novelty (indeed, the patentability) of a product may not necessarily render the process for making it patentable, no deliberation on the obviousness of a series of manipulative processes can ever be made without considering the nature of the result achieved. Where the result (however "new" by virtue of use of a new starting material) is only that which the prior art would lead the skilled artisan to expect, a finding of obviousness may be appropriate. Where, as here, virtually nothing was known about precisely how naturally-occurring glycosylated human erythropoietin comes into existence in the human body and there was no substantial basis in the art for believing that the in vivo active material could be made in any recombinant system, the successful result of the practice of Applicant's claimed invention is certainly relevant and material to obviousness considerations. Alternately stated, a result cannot transform to nonobvious a process which is concededly obvious to begin with, but the fact that a process succeeds in providing a desired result in the absence of a substantial basis in the art for expecting it to succeed is highly probative on the issue of nonobviousness.

3. The Lack of Relevance of the Talmadge et al. Reference

Attached hereto as Exhibit "D" is a copy of the Talmadge et al. reference cited by the Examiner as pertinent to process claims initially presented during prosecution of the '008 Patent. The disclosures of this reference are conspicuously distinct from the subject matter herein claimed. Whatever a skilled artisan might have understood from the reference concerning E.coli processing of endogenous and exogenous "secretory" signal sequences incorporated into fusion genes and resulting in transported fusion proteins, the disclosures are entirely silent concerning recombinant production of glycoproteins. They thus provide no suggestion to practice the processes of claims 65-69, nor any reasonable expectation that the practice of such processes would succeed in providing an in vivo biologically active product.

4. Lack of Relevance of Prior Art References Disclosing Recombinant Glycoprotein Production

In an attempt to facilitate early consideration of all patentability issues, Applicant has caused a computer-assisted search to be performed in "Medline" and "Chemical Abstracts" data bases for publications which may have relevance to the recombinant preparation of human obligate glycoproteins in in vivo biologically active form.

The general format of the search involved development of four "Concepts", each of which incorporated specific alternative search terms. The concepts were combined in various ways to provide input composite search terms within the two data bases. Concept No. 1 ("Recombinant") was defined to embrace recombinant, genetic..., engineer...,

molecular cloning, cloning/cloned, rDNA, cDNA, rErythropoietin, biotechnolog..., mRNA (Medline only), DNA biosynthesis (Medline only), recombinant protein(s). Concept No. 2 ("Proteins") was defined to embrace membrane proteins, surface proteins, receptor(s), trypanosome, clathrin, fibronectin, laminin, glycoproteins, amyloid, asialoglycoproteins, avidin, csf, hemopexin, inhibin, lactoferrin, mucoprotein, mucins, peptidoglycan, haptoglobin, protein c, proteoglycans, thrombopoietin, thryoglobulin, glycosylat..., carbohydrate structure, carbohydrate conformation. Concept No. 3 ("Cell Lines") was defined to embrace CHO, chinese hamster ovar..., CV1, BSC1, BHK, COS. Concept No. 4 ("Mammalian") was defined to embrace human and mammal. Medline searches for the period 1966-1984 were conducted for the composite of the concepts "recombinant" X "proteins" X "cell lines" (revealing 62 abstracts) and "recombinant" X "proteins" X "mammalian" plus "expression" (revealing 178 abstracts). Similarly, Chemical Abstract searches for the period 1963-1984 were based on the composites "recombinant" X "protein" X "cell lines"/-"mammalian" (providing 49 abstracts) and "recombinant" X "proteins" (excluding the above 49 abstracts and in turn providing 65 abstracts).

Copies of the search reports generated are attached as Exhibit "E" hereto. On these reports, Applicant's counsel has marked with a red "X" the reference which appeared to be relevant.

As set out in greater detail in the PTO-1449 Statement scheduled to be submitted imminently, the references generally dealt with recombinant expression of non-human glycoproteins, or recombinant expression of human

glycoproteins which are not obligate glycoproteins and do not require glycosylation for in vivo activity, or recombinant expression of fragments of human obligate glycoproteins. The only reference located which appeared to relate to recombinant production of an in vivo biologically active obligate human glycoprotein was Collen et al., J.Pharm. & Expt. Therapeutics, 231, 146-152 (1984) relating to tissue plasminogen activator. A copy of the publication is attached hereto as Exhibit "F".

The Collen et al. article (accepted for publication and published well after Applicant's initial description of COS cell expression and in vivo biological activity reported in parent application Serial Nos. 561,024 and 582,185) describes thrombolytic in vivo biological activity versus rabbit jugular vein thrombosis for recombinant human tissue-type plasminogen activator (tPA). Naturally occurring tPA is believed by applicant to share with erythropoietin the characteristic of being an obligate human glycoprotein. The reference does not describe how the recombinant mammalian host cell expression product was prepared but rather cites to Pennica et al., Nature, 301, 214-221 (1983) for this purpose. (See page 147, Methods and Materials, line 2.) The cited Pennica et al. reference is attached as Exhibit "G" hereto. Despite its characterization in Collen et al. as providing a description of mammalian cell expression of tPA, however, the 1983 Pennica et al. reference deals exclusively with non-glycosylated E.coli expression products (see penultimate paragraph on page 220) and, of course, includes no data suggesting in vivo biological activity for the E.coli-derived products. Thus Pennica et al. contains no disclosure or suggestion of

successful practice of a process for production of an obligate human glycoprotein which might be at all analogous to that set out in claims 65-69.

In a subsequent attempt to determine whether published patent applications might exist concerning mammalian cell production of recombinant human tPA, a search was conducted for such applications in the Derwent World Patents Index data base. Three published European Patent Applications filed by Genentech were located and are attached hereto as Exhibits "H", "I" and "J".

EPO 0 093 619 was published in November, 1983 (and was ultimately based on U.S. Patent Applications dating back through May, 1982). This document, like Pennica et al., contains no description of use of mammalian host cell expression systems for tPA production. The only clear mention of such systems was entirely speculative and appears in the "Summary of the Invention" at page 7:

> In addition, depending upon the host cell, the human tissue plasminogen activator hereof may contain associated glycosylation to a greater or lesser extent compared with the native material. (Emphasis supplied)

EPO Applications 0 117 059 and 0 117 060 were assertedly based on January, 1983 U.S. filings and published in late August of 1984. These publications address the production of tPA in mammalian host cells but they contain no reference to glycosylation of the recombinant products nor to any successful assays of in vivo biological activity. Thus, the Genentech published patent applications provide no demonstration of the production of an obligate

human glycoprotein such as might give rise, by analogy, to any reasonable expectation of success in the practice of the methods of present claims 65-69.

Applicant submits that the results of the above-described searches and analysis provide a clear indication that the claimed methods as practiced in 1983 were among the first, if not the first, instances of the successful production of an in vivo biologically active obligate human glycoprotein. Of course, whether Applicant was in fact absolutely the first to succeed in this respect is not outcome determinative of patentability of the present claims. It is possible that an instance of successful mammalian cell expression of such an active protein might have been reported at a time prior to Applicant's work and that the report simply escaped detection in the searches described above. Whether or not this is the case, however, it must be abundantly clear that there did not exist any body of information in the art which would be at all analogous to that existing in the Durden case, providing a basis for asserting that the transformation/transfection, transcription, translation, glycosylation and isolation as described by the present claims could reasonably have been expected to succeed in yielding a human erythropoietin product having the amino acid sequence and glycosylation needed for in vivo biological activity.

Applicant respectfully submits that the processes herein claimed were in no way obvious when originally practiced by Applicant and, accordingly, that no proper basis exists for rejection of the claims under 35 U.S.C. §103. Allowance of the claims is in complete legal harmony

with the ruling of the C.A.F.C. in In re Durden because the process herein claimed could not have been expected to provide the valuable product attained.

CONCLUSION

The foregoing amendments and remarks are believed to establish that claims 65-69 are in condition for allowance and an early notice thereof is solicited.

Respectfully submitted,

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May 24, 1988

IN THE UNITED STATES PATENT
AND TRADEMARK OFFICE

Application of	)	"Production of Erythropoietin"
FU-KUEN LIN	)	
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CERTIFICATE OF MAILING

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

Sir:

I hereby certify that this correspondence is being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on May 24, 1988.

Respectfully submitted,

MARSHALL, O'TOOLE, GERSTEIN,
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May 24, 1988