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PATENT & TRADEMARK OFFICE

EXPRESS MAIL NO.: EV335855697US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BOX PATENT EXT.

In re: U.S. Patent No. 5,356,804

Patentee : Robert DESNICK, et al.

Issue Date: October 18, 1994 **Attorney Docket No.:6923-005 (10228-007)**

FEE TRANSMITTAL LETTER FOR
REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

RECEIVED
JUN 25 2003
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Director of the United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
BOX PATENT EXT.

Sir:

Transmitted herewith is a Request for Extension of Patent Term Under 35 U.S.C. §156 for U.S. Patent No. 5,356,804, accompanied by two additional copies. The undersigned attorney for Applicant hereby states that these copies are certified to be duplicates of the original. Each copy contains the following exhibits:

Exhibit A	Assignment and Recordation
Exhibit B	Product Label
Exhibit C	Approval Letter
Exhibit D	U.S. Patent No. 5,356,804
Exhibit E	USPTO Maintenance Fee Record
Exhibit F	Regulatory Activities

Please charge the $1,120.00 fee to Deposit Account No. 16-1150. The Director is hereby authorized to charge any additional fees, which may be required, or credit any overpayment to Deposit Account No. 16-1150.

Respectfully submitted,

Date: June 20, 2003

Anthony M. Insogna 35,203
(Reg. No.)
PENNIE & EDMONDS LLP
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(212) 790-9090

2003E-0406

APP I

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Patentee : Robert DESNICK, et al.

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Sir:

Pursuant to Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, and in accordance with the provisions in 35 U.S.C. § 156 and 37 C.F.R. §§ 1.710 et seq., Mount Sinai School of Medicine of the City of New York ("Mt. Sinai"), through the undersigned, represents that it is the owner of record of United States Patent No. 5,356,804 (the "'804 Patent") and hereby requests an extension of the patent term thereof. A copy of the United States Patent and Trademark Office ("USPTO") records confirming that title resides in the Mount Sinai School of Medicine of the City of New York is attached hereto as Exhibit A.

The following information is submitted in accordance with 35 U.S.C. § 156 and 37 C.F.R. §§ 1.740 et seq. The sections of this application are numbered in a manner corresponding with the numbering of subparagraphs (1) to (15) of 37 C.F.R. § 1.740(a).

(1) "A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics."

The approved product is FABRAZYME® (agalsidase beta). The generic name for the approved product is recombinant human α-galactosidase A. FABRAZYME® agalsidase

beta has the same amino acid sequence as the native human protein. Purified agalsidase beta is a homodimeric glycoprotein with a molecular weight of approximately 100 KD. The mature protein is comprised of two subunits of 391 amino acids (approx. 51 KD each), each of which contains three N-linked glycosylation sites.

FABRAZYME® agalsidase beta is manufactured and distributed under a license to the '804 patent by Genzyme Corporation, One Kendall Square, Cambridge, MA 02139 ("Genzyme"). Genzyme was the owner and submitter of the IND and BLA (PLA) referenced herein. Further information identifying this product is provided in the product label attached hereto as Exhibit B.

(2) "A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred."

Regulatory review of Genzyme's BLA (formerly PLA) occurred under Section 351(a) of the Public Health Service Act, Title 42, United States Code.

(3) "An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred."

On April 24, 2003, the FDA issued Department of Health and Human Services U.S. License No. 1596 to Genzyme Corporation, in accordance with the provisions of Section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products, permitting the first commercial marketing or use of Genzyme's FABRAZYME® product. A copy of the approval letter is attached hereto as Exhibit C.

(4) "In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum- Toxin Act, or a statement of when the active

ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved."

The sole active ingredient in FABRAZYME® is agalsidase beta. No product containing agalsidase beta has been previously approved for commercial marketing or use under the Food, Drug and Cosmetic Act, the Public Health Service Act or the Virus-Serum- Toxin Act.

(5) "A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the last day on which the application could be submitted."

This application is being submitted within the sixty day period following FDA issuance of the FABRAZYME® (agalsidase beta) produce license on April 24, 2003. The last day on which this submission can be made is June 23, 2003.

(6) "A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration."

U.S. Patent No. 5,356,804
Robert J. Desnick, David F. Bishop and Yiannis A. Ioannou, inventors
Issue Date: October 18, 1994
Expiration Date: October 18, 2011

(7) "A copy of the patent for which an extension is being sought including the entire specification (including claims) and drawings."

A copy of U.S. Patent No. 5,356,804 is attached as Exhibit D.

(8)"A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or re-examination certificate issued in the patent."

The '804 Patent issued on October 18, 1994, and the first maintenance fee was paid on February 11, 1998. The second maintenance fee was paid on April 18, 2002. A copy of the USPTO maintenance fee record for this patent is attached as Exhibit E. No disclaimer, certificate of correction or re-examination certificate has issued in connection with the '804 Patent.

(9)"A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on:
(i) The approved product, if the listed claims include any claim to the approved product;
(ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and
(iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product."

Claims 1-9 of the '804 Patent are directed to methods for manufacturing recombinant human α-galactosidase A, and claims 10-17 relate to cells used to manufacture recombinant human α-galactosidase A. The following claim chart shows how each applicable patent claim reads on Genzyme's method of manufacturing the approved product:

1. A method for producing human .alpha.-galactosidase A comprising:	Genzyme's manufacturing method produces recombinant human α-galactosidase A as follows:
(a) culturing a mammalian cell containing a chromosomally integrated nucleotide sequence encoding human .alpha.-galactosidase A controlled by	Genzyme cultures Chinese hamster ovary cells (CHO cells) which contain a chromosomally integrated DNA sequence encoding human α-galactosidase A, under

a regulatory sequence that promotes gene expression and a selectable marker controlled by the same or different regulatory sequence, so that the .alpha.-galactosidase A nucleotide sequence is stably overexpressed and an enzymatically active .alpha.-galactosidase A enzyme is secreted by the mammalian cell; and	the control of a promoter and a selectable marker gene. The α-galactosidase A is overexpressed by the CHO cells and is secreted in an enzymatically-active form.
(b) isolating enzymatically active .alpha.-galactosidase A enzyme from the mammalian cell culture.	Genzyme's manufacturing method uses purification methods to isolate the enzymatically-active α-galactosidase A from the CHO cell culture.
2. The method according to claim 1 wherein, in the presence of selection, the chromosomally integrated nucleotide sequences are amplified.	Genzyme's manufacturing method uses the MTX/DHFR selection system to amplify the desired chromosomally integrated sequences.
3. The method according to claim 1 in which the nucleotide sequence encoding human .alpha.-galactosidase A encodes the amino acid sequence depicted in FIGS. 1A-1C [SEQ ID No: 2] from amino acid residue number 1 to 430.	Genzyme's CHO cells contain a nucleotide sequence encoding residues 1-430 of the amino acid sequence depicted in SEQ ID No. 2. Residues 1-30 comprise a "leader" which is translated and then cleaved by the CHO cells.
4. The method according to claim 1 in which the nucleotide sequence encoding human .alpha.-galactosidase A encodes the amino acid sequence depicted in FIGS. 1A-1C [SEQ. ID No. 1] from amino acid[residue number 31 to 430.	Genzyme's recombinant CHO cells contain a nucleotide sequence encoding residues 31-430 depicted in SEQ. ID No. 1, which represents the "mature" form of the enzyme after the "leader" has been cleaved.
7. The method according to claim 1 in which the selectable marker is dihydrofolate	Genzyme's CHO cells include the DHFR gene as a selectable marker.

reductase.	
8. The method according to claim 2 in which the selectable marker is dihydrofolate reductase and the selection is methotrexate.	Genzyme's CHO cells include the DHFR gene as a selectable marker, and its manufacturing method uses MTX to select for transformants.
9. The method according to claim 1 in which the mammalian cell is a Chinese hamster ovary cell line.	Genzyme's manufacturing method uses a CHO cell line.
10. A mammalian cell comprising a chromosomally integrated nucleotide sequence encoding human .alpha.-galactosidase A controlled by a regulatory sequence that promotes gene expression and a selectable marker controlled by the same or different regulatory sequence, so that the .alpha.-galactosidase A nucleotide sequence is stably overexpressed and an enzymatically active .alpha.-galactosidase A enzyme is secreted by the mammalian cell.	Genzyme's manufacturing method uses a mammalian cell as set forth in claim 10 (see description above).
11. The mammalian cell of claim 10 wherein the chromosomally integrated nucleotide sequences are amplified.	Genzyme's manufacturing method uses such a cell (as described above).
12. The mammalian cell according to claim 10 in which the nucleotide sequence encoding human .alpha.-galactosidase A encodes the amino acid sequence depicted in FIGS. 1A-1C [SEQ ID No: 2] from amino acid residue number 1 to 430.	Genzyme's manufacturing method uses such a cell (as described above).
13. The mammalian cell according to claim 10 in which the nucleotide sequence	Genzyme's manufacturing method uses such a cell (as described above).

encoding human .alpha.-galactosidase A encodes the amino acid sequence depicted in FIG. 1A [SEQ. ID No. 1] from amino acid residue number 31 to 430.	
16. The mammalian cell according to claim 10 in which the selectable marker is dihydrofolate reductase.	Genzyme's manufacturing method uses such a cell (as described above).
17. The mammalian cell according to claim in which the mammalian cell is a Chinese hamster ovary cell line.	Genzyme's manufacturing method uses such a cell (as described above).

(10) "A statement, beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product:

(A) The effective date of the investigational new drug (IND) application and the IND number;

(B) The date on which a new drug application (NDA) or a Produce License Application (PLA) was initially submitted and the NDA or PLA number; and

(C) The date on which the NDA was approved or the Product License issued."

(A) Genzyme filed an Investigational New Drug (IND) application, no. BB IND 7616, having an effective date of April 9, 1998, directed to Alpha Galactosidase A (Human Recombinant).

(B) Genzyme submitted its PLA, no. STN BL 103979/0, on June 23, 2000.

(C) The aforementioned PLA (which had been re-designated as a BLA) was approved and Produce License no. 1596 was issued thereon on April 24, 2003. (Exhibit C).

(11)"A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities."

Attached is a chronology that briefly describes the significant regulatory activities and relevant dates associated with Genzyme's efforts to seek and obtain licensing and approval of FABRAZYME® agalsidase beta. (Exhibit F).

(12) "A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined."

Statement of Eligibility for Patent Term Extension – 37 C.F.R. § 1.740(a)(12)

It is the opinion of the applicant that the '804 Patent is eligible for an extension pursuant to 35 U.S.C. § 156(a) and the applicable provisions of 37 C.F.R. §§ 1.710 et. seq. Pursuant to calculations made in accordance with 37 C.F.R. § 1.775, the '804 Patent is entitled to a term extension of **1,438 days** (the "Term Extension Period"). The Term Extension Period was determined in accordance with 37 C.F.R. § 1.775 as follows:

Length of Regulatory Review Period

Pursuant to Section 1.775(c), the length of the regulatory review period is *1,841 days*, representing the sum of (1) the number of days in the period beginning on the Effective Date of the IND (April 9, 1998) and ending on the Submission Date of the BLA (June 23, 2000)(*806 days*) and (2) the number of days in the period beginning on the Submission Date of the BLA (June 23, 2000) and ending on the date that the Product License was issued (April 24, 2003)(*1035 days*).

Length of Patent Term Extension

Pursuant to Section 1.775 (d)(1), a total of *403 days* were subtracted from the *1,841-day* length of the Regulatory Review Period, as follows:

(i) *0 days* were prior to the date on which the '804 Patent issued;

(ii) *0 days* during which the applicant did not act with due diligence; and

(iii) *403 days* representing one-half the number of days (*806 days*) remaining in the period defined by paragraph (c)(1) after which a total of *0 days* were subtracted in accordance with paragraphs (d)(1)(i) and (d)(1)(ii).

Thus, the period calculated pursuant to this section (d)(1) is *1,438 days*.

The period calculated under Section 1.775(d)(2), by adding 1,438 days to the original October 18, 2011, expiration date of the 804 Patent, ends on *September 25, 2015*.

The period calculated under Section 1.775(d)(3), by adding 14 years to the date of approval of the application under section 351 of the Public Health Service Act, ends on *April 24, 2017*.

The date selected under Section 1.775(d)(4), by comparing the two dates stated immediately above and selecting the earlier, is *September 25, 2015*.

Because the '804 Patent issued after September 24, 1984, the date determined under Section 1.775(d)(5) is arrived at by adding 5 years to the original expiration date of the '804 Patent (October18, 2011), and comparing that date (October 18, 2016) to the date determined pursuant to Section 1.775(d)(4), resulting in selection of ***September 25, 2015*** as the earlier date and thus the date to which the term of the '804 Patent should be extended.

(13) *"A statement that applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to any determination of entitlement to the extension sought."*

Applicant, through its undersigned representative, hereby acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to any determination of entitlement to the extension sought.

(14)"The prescribed fee for receiving and acting upon the application for extension."

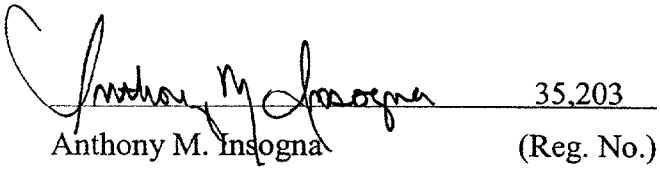
Pursuant to 37 C.F.R. § 1.20(j)(1), the prescribed fee for receiving and acting upon this application is $1,120.00. The Director is authorized to charge this fee and any additional fees, or credit any overpayment, to Deposit Account No. 16-1150.

(15)"The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed."

Please direct all inquires and correspondence relating to this application for patent term extension to the undersigned:

Respectfully submitted,

Date: June 20, 2003



35,203

Anthony M. Insogna (Reg. No.)

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ASSOCIATE POWER OF ATTORNEY

Director of the United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
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Sir:

Please recognize Anthony M. Insogna, Registration No. 35,203, whose address is Pennie & Edmonds, 1155 Avenue of the Americas, New York, NY 10036-2711, as associate attorney in the above-identified patent.

Respectfully submitted,

PENNIE & EDMONDS LLP
Attorneys for Patentee

Date: June 20, 2003

John J. Lauter 27,814 (Reg. No.)