DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125291/0

BLA APPROVAL
May 24, 2010

Genzyme Corporation
ATTENTION: Alexander Kuta, Ph.D.
Group Vice President, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Dr. Kuta:

Please refer to your biologics license application (BLA), dated and received May 30, 2008, submitted under section 351 of the Public Health Service Act for Lumizyme (alglucosidase alfa).

We acknowledge receipt of your amendments dated June 2, 4, 13, and 25, July 1, 2, 18, 24, 25, and 29, August 6, 8, 15, 18, 19, 20, 22, 26, and 29, September 8, 16, 22, 23, 24, 25, and 26, October 2, 8, 10, 14, 15, 16, and 29, November 4 and 7, December 4, 9, 11, 17, 19, and 23, 2008, January 9, 16, 22, 26, and 30, February 6, 9, 13, 19, 20, 24, and 25, March 5, 12, 20, and 31, April 1, 6, 8, 16, and 30, May 15 and 21, June 9, 11, 12, 22, and 30, July 2, 13, 14, 22, and 31, August 10, 13, 14, and 28, September 11, 21, 22, and 25, October 16 and 27, November 20, December 4, 16, 17, 30, and 31, 2009, and January 13, 25, and 28, February 11, 12, and 22, March 9, 11, 15, 17, 19, 24, and 30, April 1, 6, 7, 8, 14, and 21, May 6, 12, 21, and 24, 2010.

The December 16, 2009, amendment constituted a complete response to our November 13, 2009, action letter.

We have approved your BLA for Lumizyme (alglucosidase alfa) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Lumizyme (alglucosidase alfa) under your existing Department of Health and Human Services U.S. License No. 1596. Lumizyme (alglucosidase alfa) is indicated for patients 8 years and older with late (non-infantile) onset Pompe disease (GAA deficiency) who do not have evidence of cardiac hypertrophy. The safety and efficacy of Lumizyme (alglucosidase alfa) have not been evaluated in controlled clinical trials in infantile-onset patients, or in late (non-infantile) onset patients less than 8 years of age.

Under this license, you are approved to manufacture Lumizyme (alglucosidase alfa) drug substance at Genzyme Flanders in Geel, Belgium. The final formulated product will be manufactured, filled, and packaged at Genzyme Ireland in Waterford, Ireland. You may label your product with the proprietary name Lumizyme and market it in vials containing 50 mg of lyophilized product.

The dating period for Lumizyme (alglucosidase alfa) shall be 24 months from the date of manufacture when stored at 2 to 8 ºC. The date of manufacture shall be defined as the date of [redacted] (b) (4) of the formulated drug product. The dating period for your drug substance shall be 4 weeks when stored at 6 to 10 ºC.

You currently are not required to submit samples of future lots of Lumizyme (alglucosidase alfa) to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in the manufacturing, testing, packaging or labeling of Lumizyme (alglucosidase alfa), or in the manufacturing facilities.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this biological product for this indication has received orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risks of anaphylaxis and severe allergic reactions, and signals of severe cutaneous and systemic immune complex-mediated reactions with Lumizyme (alglucosidase alfa) treatment.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1. A retrospective immunogenicity study based on the pattern of antibody responses that may predict the development of anaphylaxis, allergic reactions, and immune-complex mediated reactions in patients enrolled in the Late Onset Treatment Study (LOTS) and LOTS Extension Studies.

   The timetable you submitted on May 6, 2010, states that you will conduct this study according to the following timetable:

   Final Protocol and Analytic Plan Submission: **October 29, 2010**
   Study Completion Date: **August 29, 2011**
   Final Report Submission: **December 30, 2011**

2. A prospective safety study conducted within the ongoing Pompe Registry to assess the known serious risks of anaphylaxis and severe allergic reactions, and signals of severe cutaneous and systemic immune complex-mediated reactions with Lumizyme (alglucosidase alfa) treatment.

   The timetable you submitted on May 6, 2010, states that you will conduct this study according to the following timetable:

   Final Protocol Submission: **December 30, 2010**
   Study Completion Date: **September 30, 2022**
   Final Report Submission: **April 20, 2023**

Submit the protocols to your IND 010780, with a cross-reference letter to this BLA, STN BL 125291. Submit all final reports to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS OF SECTION 506B

We acknowledge your written commitments as described in your letter of May 6, 2010, as outlined below:

3. A retrospective study of patients enrolled in the LOTS and LOTS Extension Studies whose efficacy responses (i.e., high performance or poor performance) as assessed by the 6 minute walk test (6MWT) and/or % predicted forced vital capacity (FVC) appeared to have been affected by the pattern of their antibody response.

   Final Protocol and Analytic Plan Submission: **October 29, 2010**
   Study Completion Date: **August 29, 2011**
   Final Report Submission: **December 30, 2011**

4. A long-term follow-up study to evaluate long-term efficacy and immunogenicity outcomes in a subpopulation of patients in LOTS and LOTS Extension Studies whose response to Lumizyme (alglucosidase alfa) is associated with substantial improvement over baseline in the 6 minute walk test (6MWT) results. This study will be conducted as a sub-study within the ongoing Pompe Registry.

   Final Protocol Submission: **September 30, 2010**
   Study Completion Date: **February 28, 2022**
   Final Report Submission: **September 30, 2022**

5. As part of the ongoing Pompe Registry, prospective outcome data will be collected in patients enrolled in the Registry to assess the long-term efficacy of Lumizyme (alglucosidase alfa).

   Final Report Submission: **September 30, 2022**

6. A prospective pharmacokinetic (PK) study conducted within the ongoing Pompe Registry study to characterize the pharmacokinetics of Lumizyme (alglucosidase alfa) in pediatric patients in the age range of 8 years to 18 years.

   Final Protocol Submission: **August 30, 2010**
   Study Completion Date: **August 30, 2014**
   Final Report Submission: **March 30, 2015**

POSTMARKETING COMMITMENTS NOT SUBJECT TO REPORTING REQUIREMENTS OF SECTION 506B

We acknowledge your written commitments as described in your letter of May 6, 2010, as outlined below:

7. To evaluate the use of the (b) (4) method as a release test for glycan profiling of the drug substance.

   Final Report Submission: **July 30, 2010**

8. To develop an analytical method to monitor (b) (4) (b) (4) evaluate risk to product quality and propose risk mitigation strategies.

   Final Report Submission: **December 30, 2010**

9. To establish in process control limits for cell viability during the (b) (4) period using the data collected from four upcoming 4000 L cell culture runs.

   Final Report Submission: **June 30, 2010**

10. To develop and qualify an in-house 4000 L reference standard.

    Final Report Submission: **September 30, 2011**

11. To develop and implement more sensitive and quantitative methods to enhance the detectability and quantitation of degradation products of rhGAA protein, as well as (b) (4).

    Final Report Submission: **December 30, 2010**

12. To add the (b) (4) test to the stability specifications for 4000 L drug substance.

    Final Report Submission: **December 31, 2010**

13. To add the (b) (4) test to the release and stability specifications for 4000 L drug product.

    Final Report Submission: **December 31, 2011**

14. To re-evaluate and optimize the (b) (4) hold time to improve (b) (4) (b) (4) species for the 4000 L product.

    Final Report Submission: **July 30, 2010**

15. To re-evaluate and revise the acceptance criterion for Km measured by the (b) (4) (b) (4)

    Final Report Submission: **December 30, 2010**

16. To include in the annual rhGAA Drug Product stability protocol, derived from drug substance produced at the 4000 L scale, an accelerated storage condition of 25 ± 2°C and 60 ± 5% relative humidity (RH).

    Final Report Submission: **May 28, 2010**

17. To qualify the (b) (4) for its intended use by performing an equivalency test between the D value of (b) (4) and (b) (4) (b) (4)

    Final Report Submission: **May 28, 2010**

We request that you submit clinical protocols to your IND 010780, with a cross-reference letter to this BLA, STN BL 125291. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this BLA, STN BL 125291. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing commitments as appropriate:

- **POSTMARKETING COMMITMENT PROTOCOL**
- **POSTMARKEING COMMITMENT – FINAL REPORT**
- **POSTMARKETING CORRESPONDENCE**
- **ANNUAL STATUS REPORTING OF POSTMARKETING COMMITMENTS**

For each postmarketing commitment subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report. The status report for each commitment should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including the patient accrual rate (i.e., number enrolled to date and the total planned enrollment); and,
- a revised schedule if the scheduled milestones have changed and an explanation of the basis for the revision.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). The details of the REMS requirements were outlined in our complete response letter dated February 27, 2009.

Pursuant to 505-1(f)(1), we have determined that Lumizyme (alglucosidase alfa) can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate the risk of rapid disease progression in infantile-onset Pompe disease patients and patients with late (non-infantile) onset disease less than 8 years of age, the risks of anaphylaxis and severe allergic reactions, and potential risks of severe cutaneous and systemic immune mediated reactions as listed in the labeling. The elements to assure safe use will ensure that Lumizyme (alglucosidase alfa) will only be dispensed to patients with evidence or other documentation of safe-use conditions, require prescribers of Lumizyme (alglucosidase alfa) to be specially certified, and require that Lumizyme (alglucosidase alfa) will only be dispensed by pharmacies, practitioners, or healthcare settings that are specially certified.

Your proposed REMS, submitted on May 24, 2010, and appended to this letter, is approved. The REMS consists of a communication plan, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include, but is not limited to, the following:

a. The number of certified prescribers in the Lumizyme ACE Program that have undergone training and certification during the reporting period and cumulatively
b. The number of patients enrolled in the Lumizyme ACE Program during the reporting period and cumulatively
c. The number of certified healthcare facilities in the Lumizyme ACE program that have undergone training and certification during the reporting period and cumulatively
d. The number of healthcare facilities that have ordered/administered Lumizyme that were not enrolled in the ACE program during the reporting period and cumulatively
e. The number of prescribers and healthcare facilities who were removed from enrollment in the ACE Program during the reporting period and cumulatively due to noncompliance
f. The number of patients with infantile-onset Pompe disease who were prescribed and administered Lumizyme during the reporting period and cumulatively
g. Corrective and preventative actions taken to address noncompliance with distribution and dispensing requirements during the reporting period and cumulatively
h. A narrative summary and analyses of anaphylaxis, severe allergic reactions, and severe cutaneous and systemic immune mediated reactions reported with use of Lumizyme during the reporting interval.
i. Results of any surveys of patients', physicians', and other healthcare providers' understanding of the serious risks of Lumizyme.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(A), an assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report

required under section 506B and 21 CFR 601.70 and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

STN BL 125291
REMS ASSESSMENT

NEW SUPPLEMENT FOR STN BL 125291
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR STN BL 125291
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment

instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations sent by courier or overnight mail should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20993-0002

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling text for the package insert. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed draft labels as soon as they are available but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved STN BL 125291/0**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with labeling that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this BLA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

If you have any questions, call Wes Ishihara, Chief, Project Management Staff, at (301) 796-0069.

Sincerely,

/Julie Beitz/
Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures: REMS documents; Package Insert