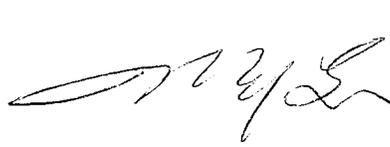


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

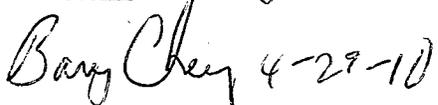
APPLICATION NUMBER:
125291

CHEMISTRY REVIEW(S)

Review Memo

From: Juhong Liu, Ph.D.  4/29/2010
Biologist
Laboratory of Chemistry
Division of Therapeutic Proteins

To: Amy Rosenberg, MD  4-29-10
Director
Division of Therapeutic Proteins

Barry Cherney, Ph.D.  4-29-10
Deputy Director
Division of Therapeutic Proteins

Through: Emanuela Lacana, Ph.D.  4/29/2010
Associate Chief
Laboratory of Chemistry
Division of Therapeutic Proteins

Subject: CMC review of STN 125291/0.98, Resubmission of Lumizyme
Manufactured at 4000L Bioreactor scale

REVIEW MEMO.....1

REVIEW SUMMARY4

INTRODUCTION AND CLINICAL BACKGROUND6

CATEGORICAL ENVIRONMENTAL EXCLUSION.....6

DRUG SUBSTANCE7

(b) (4)7

(b) (4)7

(b) (4)8

(b) (4)9

(b) (4)9

(b) (4)13

Purification Process for the 4000L Process:14

Description of Purification Process14

(b) (4)15

(b) (4)17

Validation of Drug Substance Purification Process:18

 Validation of Purification:18

 Validation of Intermediates Hold Time:22

 Cleaning Validation:23

 Validation of Viral clearance/Inactivation:24

Drug Substance Characterization:25

 Control of Drug Substance:25

 Drug Substance Release Specification:25

 Transfer of Analytical Procedures:27

Drug Substance Comparability:29

(b) (4)29

(b) (4)32

(b) (4)34

(b) (4)37

(b) (4)38

(b) (4)39

(b) (4)41

(b) (4)42

(b) (4)43

(b) (4)46

(b) (4)47

Drug Substance Stability	48
Drug Substance Reference Standard:	49
DRUG PRODUCT	50
Drug Product Manufacturing	50
Validation of Drug Product Manufacturing Process	52
Media fill	52
Validation of Formulated Drug Substance Hold Time:	52
Control of Drug Product:	54
Drug Product Specifications	54
Drug Product Comparability	56
Drug Product Stability	57
Stability of Drug Product stored at 2-8°C:	58
Accelerated stability (25 ± 2°C, 60 ± 5% RH), six month studies	58
Stability of Reconstituted Drug Product:	59
..... (b) (4)	60
OIL CONTAMINATION OF LUMIZYME AT GENZYME FLANDERS	61
Review Summary:	61
Background:	61
Component and Potential Chemical Toxicity of Oil:	62
Potential Oil Contamination on Drug Substance:	63
1. (b) (4) h overview:	63
2. Estimate of the amount of oil in (b) (4) under worst case scenario:	64
3. Estimate of the amount of oil in (b) (4):	66
4. Testing of the amount of oil in Drug Substance:	67
Potential Oil Contamination on Drug Substance Purity:	67
1. Protein impurity:	68
2. Protein Recovery:	68
3. Viral clearance:	68
Potential Oil Contamination on DS/DP Release Testing Results:	69
Corrective and Preventive Actions:	69
1. Immediate Corrective Actions:	69
2. Short-term preventive actions:	70
3. Mid-term preventive actions	70
Mineral Oil Analysis (attachment 7):	70

Review Summary

Lumizyme (recombinant human acid alpha-glucosidase, alglucosidase alfa, rhGAA) is a 110kDa, heavily glycosylated enzyme that is produced by Genzyme for Enzyme Replacement Therapy of patients with a confirmed diagnosis of Pompe's disease. In the United States, Lumizyme produced at 2000L scale is under review for the treatment of Pompe's disease in late onset patients. In most other countries, Lumizyme produced at 2000L and 4000L scale are licensed for treatment of both infantile and late onset patients.

In order to streamline the manufacture and to meet the demand of Lumizyme, Genzyme proposed to replace the 2000L scale process with the 4000L scale process in the US. In response to the Complete Response Letter issued by FDA dated November 13, 2009, regarding the deficiencies identified during the inspection of Genzyme Allston Landing facility, and as agreed upon by FDA and Genzyme, Genzyme withdraws its request for licensure of Allston Landing facility for manufacture of Lumizyme. This resubmission contains CMC, nonclinical and safety update, as well as information from the 2000L scale Lumizyme product applicable to the 4000L scale process to seek licensure of Genzyme Flanders and Waterford facilities for manufacture 4000L scale Lumizyme. The cell culture, drug substance purification and formulation are conducted at the Genzyme Flanders facility. 4000L scale Lumizyme drug product manufacturing is conducted at the Genzyme Waterford facility. In this submission, Genzyme provided description and validation of both drug substance and drug product manufacturing processes. Characterization data of drug substance and drug product were also provided. A comprehensive comparability study data with selected 2000L and 4000L scale drug substance lots were also provided.

This review focuses on the comparison of the 2000L and 4000L manufacturing processes and the potential impacts of these changes in the 4000L process on the critical attributes of the 4000L drug substance as summarized below:

There are two major changes in the purification of rhGAA drug substance in the 4000L process:

1.



2.

(b) (4)

The targeting of exogenously administered Lumizyme to the target tissues relies primarily on two critical attributes of Lumizyme.

(b) (4)

The manufacturing validation data indicate the 4000L manufacturing process is robust. Drug substance characterization/comparability data also indicate physicochemical properties of the 4000L scale drug substance are comparable to that of 2000L drug substance, with improvements of several attributes critical for product quality. Overall, the 4000L product is much improved over the 2000L product.

During the review cycle, Genzyme submitted an amendment describing between February 26, 2009 and March 18, 2010, hydraulic oil (b) (4) has leaked into the purification system and a total of (b) (4) Lumizyme drug product lots manufactured during this period may have been contaminated. Review of the analyses of these drug product lots indicates the low levels of oil in the purification process are unlikely to adversely impact product quality. The residual oil contaminant in the final drug product is extremely also low. Thus recall of the drug product is not necessary. However, it is recommended that the implementation of corrective and preventive actions be inspected during the next inspection.

67 pp withheld in full immed. after this page as (b)(4) CCI/TS.

SUMMARY BLA125291 alfa glucosidase



DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Monoclonal Antibodies
Division of Therapeutic Proteins

The Quality Team Leader's Executive Summary

From: **Emanuela Lacana, PhD**
Division of Therapeutic proteins (DTP)

Through: **Barry Cherney, PhD**
DTP Deputy Division Director
Amy Rosenberg, MD
DTP Division Director

BLA Number: **125291**
Product: **LUMIZYME (alfa glucosidase)**
Sponsor: **Genzyme Corporation**

Date of Review: **25 March, 2010**

Due Date of CDTL Memo:

I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of BLA125291 for alglucosidase alfa, manufactured by Genzyme Corporation. The data submitted in this application support the conclusion that the manufacture of alglucosidase alfa is well controlled, and leads to a product that is pure and potent. The processes used in manufacturing have been validated, and a consistent product is produced from different production runs.

Clinical studies supporting treatment of this product in patients 8 years or older with a confirmed diagnosis of Pompe disease were performed using material derived from a 2000L bioreactor. During the review of this original application, Genzyme moved the site of manufacturing from Allston Landing, Massachusetts (USA) to Geel, Flanders (Belgium) and increased the bioreactor scale from 2000L to 4000L.

(b) (4)

(u) (4)

It is recommended that this product be approved for human use (under conditions specified in the package insert).

II. APPROVAL LETTER INFORMATION

Under this license, you are approved to manufacture Alglucosidase alfa drug substance at Genzyme Corporation in Geel, Belgium. The final formulated product will be manufactured, filled, labeled, and packaged at Genzyme Corporation, Waterford, Ireland. You may label your product with the proprietary name LUMIZYME and will market it in 50 mg vials.

The dating period for Alglucosidase alfa shall be 24 months from the date of manufacture when stored at 2 to 8 °C. 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 °C. The dating period for your formulated bulk drug product shall be 6 months when stored at 6 to 10 °C. Results of ongoing stability studies should be submitted throughout the dating period, as they become available, including results of stability studies from the first three production lots. We have approved the stability protocol(s) in your license

SUMMARY BLA125291 alfa glucosidase

application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.]

You currently are not required to submit samples of future lots of 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 biologics license application for our review and written approval under 21 CFR 601.12 for any changes in the manufacturing, testing, packaging or labeling of Alglucosidase alfa, or in the manufacturing facilities.

III. POST MARKETING COMMITMENTS/POST MARKETING REQUIREMENTS

Post Marketing Commitments 1-6 relate to clinical issues.

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

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

Final Report Submission:

December 30, 2010

8. 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

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

Final Report Submission:

September 30, 2011

10. 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

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

Final Report Submission:

December 31, 2010

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

Final Report Submission:

December 31, 2011

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

Final Report Submission:

July 30, 2010

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

Final Report Submission:

December 30, 2010

14. 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 $25 \pm 2^\circ\text{C}$ and $60 \pm 5\%$ relative humidity (RH).

Final Report Submission:

May 28, 2010

IV. EXECUTIVE SUMMARY

A. Description of PRODUCT

Alglucosidase alfa (LUMIZYME) is the United States Approved Name (USAN) for the active ingredient in LUMIZYME. Alglucosidase alfa is a human acid alpha glucosidase (rhGAA), produced by recombinant DNA technology in a Chinese Hamster Ovary cell line. LUMIZYME is an enzyme that cleaves the 1,4 glycosidic bonds of glycogen and, to a lesser extent, the 1,6 glycosidic bonds. LUMIZYME is produced by Genzyme in CHO (Chinese Hamster Ovary) cells by recombinant DNA technology. The enzyme is manufactured in bioreactors at 4000L scale. Alglucosidase alfa is an (b) (4)

(b) (4) There is a (b) (4) (b) (4) that is critical for uptake of the enzyme into lysosomes.

LUMIZYME is supplied in single use 20 ml (b) (4) glass vials, stoppered with a (b) (4) stopper. Vials are filled with 50 mg of LUMIZYME (10.5 ml/vial at 5 mg/ml), the product is lyophilized and stored at 2-8°C.

Genzyme submitted a request for Categorical Exclusion from Environmental Assessment, which has been granted based on 21 CFR 25.31 (c).

B. Clinical Trial Information

LUMIZYME (rhGAA) is indicated for long term enzyme replacement therapy of patients 8 years or older with a confirmed diagnosis of Pompe disease (acid alpha glucosidase deficiency). Pompe disease is a rare genetic disease caused by a deficiency of acid alpha-glucosidase (maltase), which degrades lysosomal glycogen. This deficiency leads to accumulation of glycogen in muscle and finally to its destruction. LUMIZYME (20 mg/kg of body weight) is reconstituted with sterile Water For Injection and diluted in saline solution in infusion bags. The total volume of infusion is determined by the patient's body weight. LUMIZYME is administered to patients by intravenous infusion over a period of approximately 4 hours.

C. Stability

LUMIZYME Drug Substance is stored (b) (4) for 4 weeks and data supporting this storage condition were provided in the submission. The formulated Drug Substance can be stored up to (b) (4). The Drug Product is lyophilized in 20ml (b) (4) glass vials and the sponsor provided data supporting storage at 2-8°C for up to 24 months. The Drug Product contains no preservatives and vials are single-use. Studies conducted to evaluate the degradation pathways of alglucosidase alfa at suboptimal pH and high temperatures showed that the major pathway of degradation is (b) (4). Additionally, alglucosidase alfa may undergo (b) (4). While mechanical stress did not appear to alter the physicochemical characteristics of alglucosidase alfa, exposure to light caused degradation that could be measured by peptide mapping, SDS-PAGE and SEC-HPLC. The drug product is sensitive to light and it is

recommended that a “**protect from light**” statement is included in the package insert and on carton and container.

Genzyme conducted in-use stability studies on reconstituted drug product and on drug product diluted in saline after reconstitution. The reconstituted drug product is stable for up to 96 hrs at 2-8°C and 25°C. After dilution, the product is stable for up to 6 hrs at room temperature, passing through IV lines. Genzyme recommends administering the drug immediately after dilution, and the use of an in-line filter. Adequate data are submitted in the application to support the stability of reconstituted and diluted drug product during the time of infusion.

D. Complexity

• **Critical Quality Attributes**

- Glycosylation: Glycan chains are critical for the mechanism of action of alglucosidase alfa and clinical efficacy. (b) (4).
(b) (4) However, this assay is not very sensitive and glycan determination using (b) (4) is recommended (addressed by PMC).
- Mannose-6 phosphate and (b) (4): The presence of phosphorylated mannose is critical for clinical efficacy, (b) (4).
(b) (4) Specifications are established for the amount of mannose-6 phosphate and (b) (4) and are representative of the clinical trial material.
- Enzyme activity: Enzyme activity is critical for clinical efficacy. Enzyme activity is monitored using two release specifications involving the: (b) (4).
(b) (4)
- Cellular uptake: Cellular uptake is crucial for the function of alglucosidase alfa. In order to reduce the levels of glycogen accumulated in lysosomes, alglucosidase alfa must be internalized, (b) (4).
(b) (4)
- (b) (4)

E. Mechanism of Action

Alglucosidase alfa cleaves the 1, 4 glycosidic bonds in the glycogen that accumulates in muscle cells, and, to a lesser extent, the 1, 6 glycosidic bonds, that cause branching of glycogen. Deficiencies in the enzymatic activity of the protein lead to abnormal accumulation of glycogen in muscle cells and eventually to muscle destruction. Mutations of the gene encoding alglucosidase alfa result in reduction or complete elimination of alglucosidase alfa activity. Partial deficiency leads to disease of varying severity and at a wide age range of onset. These partial deficiencies are subdivided into nonclassical infantile, childhood, juvenile, and adult Pompe's disease. Classic infantile Pompe's patients have a median activity < 1/100 of normal activity. This essentially complete deficiency of alglucosidase alfa causes progressive lethal cardiac and skeletal muscle degeneration. Very few untreated infantile Pompe's disease patients live beyond their first birthday.

Alglucosidase alfa is an [REDACTED] (b) (4)

[REDACTED] (b) (4) The structures of the carbohydrate chains at each glycosylation site have been characterized. [REDACTED] (b) (4)

[REDACTED] Most important for the function of alglucosidase alfa is the presence of mannose-6 phosphate and, in particular, [REDACTED] (b) (4), because cellular uptake of alglucosidase alfa occurs via the mannose-6 phosphate receptor and is most efficient on binding [REDACTED] (b) (4). Upon binding to the receptor, alglucosidase alfa is internalized and directed to the lysosomal compartment of the cell, where glycogen accumulates. Once in the lysosomal compartment, the 110kDa alglucosidase alfa precursor undergoes proteolytic cleavage to generate a mature, fully active enzyme of about 76kDa.

(b) (4)

F. Manufacturing Process

Alglucosidase alfa is manufactured by recombinant DNA technology in a Chinese Hamster Ovary (CHO) cell line.

(b) (4)

(b) (4)



The drug substance is formulated in polysorbate 80, mannitol, and sodium phosphate buffer, lyophilized in Type I glass (b) (4) tubes, (b) (4)

The product is available in a 50mg presentation.

G. Comparability

Modifications to the process used to manufacture the clinical trial material were made when the commercial process was implemented, and included:

- i. New manufacturing site
- ii. Bioreactor scale-up, from 2000L to 4000L

iii.

iv.

(b) (4)

Genzyme provided extensive studies designed to demonstrate comparability of the drug substance manufactured with at the 2000L scale and the drug substance manufactured at the 4000L scale. Genzyme assessed physicochemical comparability using both release and characterization assays and performed stress degradation studies. The result of the comparability studies showed that the 2000L

and 4000L manufacturing processes yielded drug substance with similar physicochemical characteristics. The average mannose-6-phosphate content level was (b) (4) in the 4000L material, (b) (4)

(b) (4). Cellular uptake and enzyme kinetic activity assays, the latter conducted using both a surrogate and natural substrate, showed comparable assay profiles,

Minor differences were observed in (b) (4) and in percentage of (b) (4) in the (b) (4). Both attributes were slightly decreased in the 4000L material compared to the 2000L. Genzyme provided data showing that the (b) (4) did not preferentially contain species with high (b) (4) content. Additionally, Genzyme also provided animal data in a Pompe model of disease showing that these differences had no effect on biodistribution and pharmacological effect of LUMIZYME.

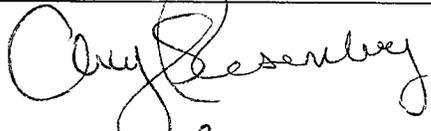
Taken together, all data submitted by Genzyme support the conclusion that the 2000L and 4000L processes manufacture materials are highly similar and that the minor differences noted are unlikely to have clinical consequences.

H. Immunogenicity

A vast majority of patients enrolled in the LOTS trial developed antibodies against the product (85-90%) and about a third of these patients also developed neutralizing antibodies, which persisted and correlated with decreased efficacy of alglucosidase alfa.

The review of module 3.2 is attached as a separate document.

V. SIGNATURE BLOCK (BLA ONLY)

Name and Title	Signature and Date
Amy Rosenberg, MD Director Division of Therapeutic Proteins	
Barry Cherney, PhD Deputy Director, Division of Therapeutic Proteins	Barry Cherney 4-29-10
Emanuela Lacana, PhD Associate Laboratory Chief, Laboratory of Chemistry, Division of Therapeutic Proteins	Emanuela Lacana 4/29/2010
Juhong Liu, PhD Laboratory of Chemistry Division of Therapeutic Proteins	 4/29/10

STN 125291/72
Review of Genzyme CMC responses to February 27, 2009 CR
and Review of CMC PMCs

Final 1

Frederick C. Mills
9-29-09

Memo

Date: July 16, 2009

Revised September 23, 2009

From: Fred Mills, Staff Scientist, DTP

Through: Barry Cherney, Deputy Director, DTP;

Barry Cherney 9-29-09

Subject: Review of STN 125291/072, May 15 2009

Review of Genzyme's CMC responses to the FDA February 27, 2009 CR letter, and review of CMC PMCs

Summary of Communications to Genzyme resulting in agreement on CMC PMCs

Communication to Genzyme July 24, 2009 in a Discipline Review Letter

Your responses to the February 27 CR letter are adequate for FDA Questions 2, 3, and 4; which pertain to:

FDA Question 2

Qualification of a reference standard for the 2000 L process

FDA Question 3

Lot release specifications for (b) (4) assay, SDS-PAGE gel assays, HPLC for measurement of total mannose-6-phosphate (M6P), HPAEC-PAD for measurement of (b) (4); and size exclusion chromatography

FDA Question 4

Revision of the system suitability criterion for the (b) (4) analytical test

FDA Question 1

(b) (4)

Review of Genzyme CMC responses to February 27, 2009 CR
and Review of CMC PMCs

excluding manufacturing runs that had deviations that potentially affected product quality.

2. The lower action limits for the (b) (4); results should be revised to more closely bracket your manufacturing experience. The proposed limits of (b) (4) standard deviations do not provide any assurance that this parameter is adequately controlled. Limits should be established based on real manufacturing experience and additional process understanding established through developmental studies not on a statistical analysis. Please revise the lower in process limit to reflect current process understanding and include your rationale for your approach and the supporting data.

Genzyme responded on August 5, 2009 by secure email and by formal submission August 13, 2009 in STN 125291/088.

The FDA then provided the following communication to Genzyme on August 10, 2009; i.e.

1. We understand that you will establish appropriate in process control limits for cell viability during (b) (4) but will require additional data in order to set these limits. Please provide an estimated time-table for establishing these limits and when this information will be submitted to the file.

2. Your proposal to specify an in process control for the lower value of the (b) (4) (b) (4) that is (b) (4) of the initial value for the Lumizyme harvest phase is acceptable.

A teleconference was held on August 11, 2009, resulting in agreement on the cell viability issue. Genzyme provided the following formal responses on August 13, 2009 in STN 125291/088.

The proposed cell viability PMC language is as follows:

“Genzyme commits 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. (b) (4)

(b) (4)

This resulted in agreement on all four of the Lumizyme CMC PMCs

Review of Genzyme CMC responses to February 27, 2009 CR
and Review of CMC PMCs

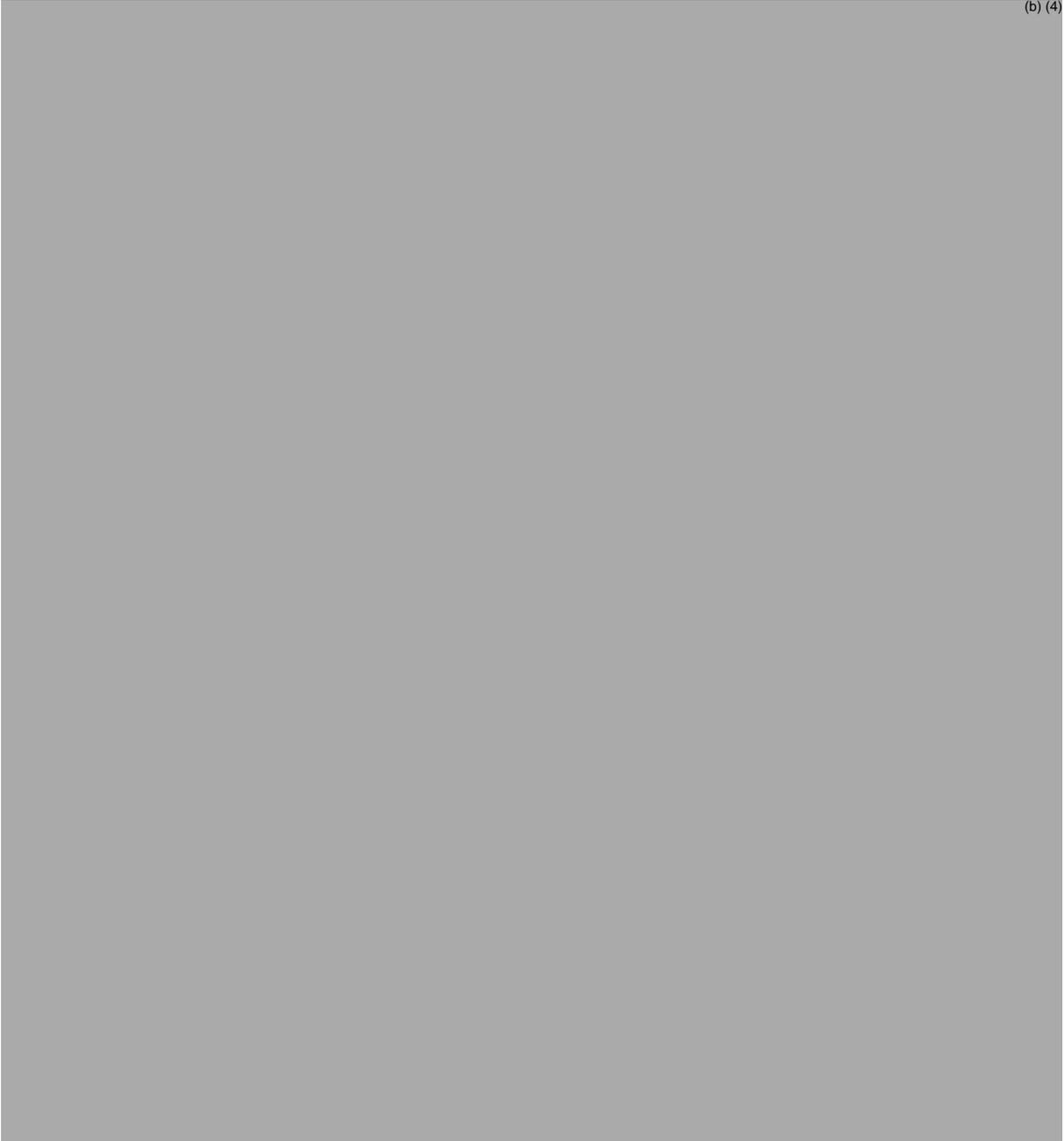
**Review of Genzyme CR response and Lumizyme CMC postmarketing
commitments**

FDA Question 1

Cell Viability is a critical parameter for controlling product quality during (b) (4)

Genzyme Response STN 125291/072, May 15 2009

(b) (4)



Genzyme responded on August 5, 2009 by secure email and by formal submission August 13, 2009 in STN 125291/088. The FDA then provided the following communication to Genzyme on August 10, 2009; i.e.

1. We understand that you will establish appropriate in process control limits for cell viability during (b) (4) but will require additional data in order to set these limits. Please provide an estimated time-table for establishing these limits and when this information will be submitted to the file.

2. Your proposal to specify an in process control for the (b) (4) that is (b) (4) of the initial value for the Lumizyme harvest phase is acceptable.

A teleconference was held on August 11, 2009, resulting in agreement on the cell viability issue. Genzyme provided the following formal responses on August 13, 2009 in STN 125291/088.

The proposed cell viability PMC language is as follows:

“Genzyme commits 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. (b) (4)

(b) (4)

Monitoring of bioreactor metabolic parameters

In their May 15, 2009 response, (b) (4)

(b) (4)

STN 125291 proposed revised specifications
Submitted 3-13-09

Final 1

Frederick Mills 4-24-09

Memo

Date: March 23, 2009
Revised March 26, 2009
Revised April 20, 2009

From: Frederick C. Mills, Staff Scientist, DTP, OBRR, CDER

To: Barry Cherney, Deputy Director, DTP, OBRR, CDER,

Barry Cherney 4-24-09

Subject : STN 125291/0 (Lumizyme) for late onset Pompe's disease;
Genzyme proposed revised specifications, submitted 3-13-09

Comments to the Sponsor

The FDA has the following comments regarding your proposed revisions to specifications for Lumizyme (STN 125291), which were communicated to the Agency on March 13, 2009

(b) (4)

15 pp Withheld in full Immed. after this page as (b)(4) CCI/TS.

Memo

From: Frederick C. Mills, Staff Scientist, DTP, OBP, CDER
To: STN125291/0, Lumizyme original licensing application
Through: Barry Cherney, Deputy Director, DTP, OBP, CDER,
Cc: Wes Ishihara, Regulatory Project Manager, DGP, CDER

*Frederick C. Mills
2-26-09
Fred Mills
2-26-09*

Subject: STN125291/0 Lumizyme licensing application
Summary of Allston Landing 2000L bioreactor production failure, with reference to a similar event in a 4000L bioreactor in Geel, Belgium.

Date: February 23, 2009

Executive Summary

During validation of the 4000 L Myozyme process at Genzyme's Geel, Belgium facility, rapid cell death was observed during bioreactor run 20810310 (b) (4)

Several weeks later, as 2000L Myozyme bioreactor runs were in progress in Genzyme's Allston Landing, MA facility (b) (4) November 14, 2009), the run in bioreactor 7B (lot number 11013526) experienced a rapid cell death event. Because of similarities between events at Geel and Allston, Genzyme immediately terminated this bioreactor run on (b) (4) The run in Bioreactor 7A (9828273) was continued and terminated as per protocol (b) (4)

(b) (4)

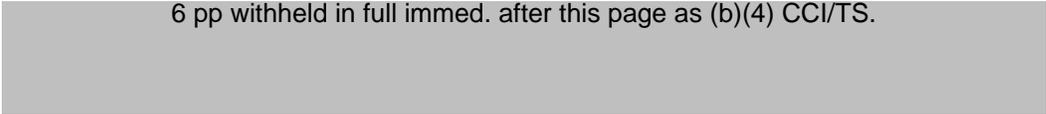
processes in the USA and in Europe. Indeed, it was made apparent that Genzyme had recently commissioned a new supplier of some raw materials.

(b) (4)



From supply/demand projections provided by Genzyme, it is clear that loss of material associated with the 7B reactor incident would severely impact supply during the first part of 2009, especially if EMEA approval of the 4000L process material is delayed until May 1, 2009. To manage the tight Myozyme / Lumizyme supply, Genzyme has adopted the strategy of asking adult Pompe's patients to skip one dose per month.

6 pp withheld in full immed. after this page as (b)(4) CCI/TS.



To manage the tight Myozyme / Lumizyme supply, Genzyme has adopted the strategy of asking adult Pompe's patients to skip one dose per month.

STN125291/0 Lumizyme CMC review

Final ¹

Frederick C. Mills 2-9-09

Memo

Date: November 4, 2008
January 6, 2008 revised
January 15, 2008 revised
January 26, 2009, revised
January 30- February 5, 2009, revised
February 9, revised BC

From: Frederick C. Mills, Staff Scientist, DTP, OBRR, CDER

To: Barry Cherney, Deputy Director, DTP, OBR, CDER, Amy Rosenberg, Director
DTP, OBR, CDER *Barry Cherney* 2-9-09

Subject : STN 125291/0 Myozyme (Lumizyme) for late onset Pompe's disease;
2000 L process CMC review

Table of Contents

Heading	Page
Post marketing commitments	4
Executive summary	8
Drug Substance Process	9
Drug Substance Specifications	11
Comparison of 160 L versus 2000 L Drug Substance manufacturing History for quality attributes expected to have important Safety and Efficacy impacts	14
Drug Substance Stability	16
Drug Product Manufacturing	16
Drug Product Specifications	17
Durg Product Comparability considerations	18
Drug Product Stability	19
CMC Review of STN125191	21
Introduction	21
Comparison of Manufacturing for the 160L and 2000L processes	31
General Derivation of Specifications	44
Proposed Specifications	45
Drug Substance Specifications, Tabulated Comments	48
Discussion of Data Important for the comparability of the 160L and 2000L processes	50
	51
	54
	55
	56
	57
	59
	61
	62
	63
	68
	69
	73
	74
Drug Substance Stability	74

Table of Contents (continued)

Heading	Page
Drug Product	77
Drug Product Manufacturing	77
Drug Product Specifications	82
Drug Product Specifications, tabulated comments	83
Drug Product Batch Analysis	85
Glycogen kinetics	85
Drug Substance and Drug Product Kd determinations	87
Intracellular Processing	88
Additional tests (SDS PAGE purity)	90
(b) (4) analysis of Drug Product	91
Drug Product Stability	92
Drug Product Stability 2-8 °C storage (real time)	93
Drug Product Accelerated Stability Studies	96
Reconstitution Stability Studies	98
(b) (4)	101
(b) (4)	101
(b) (4)	103
(review of September 19, 2008 Genzyme Submission)	

Post-Marketing Commitments and rationale

1. To provide data supporting the limits on cell viability (b) (4) for the bioreactor harvests. Data supporting the proposed limits on cell viability will be submitted to the FDA by

Rationale

(b) (4)

(b) (4) Lose of cell viability might translate to significant adverse impact on product quality so the established control limits should reflect established process capability. In order to justify this specification, please provide data such as the time course of viability during the harvest phase for runs that adequately represent the range of viabilities seen with the 2000 L process.

(b) (4)

Rationale

(self explanatory)

3. To re-evaluate and revise the acceptance criteria for drug substance and drug product specifications consistent with manufacturing process capability and considerations of safety and efficacy. Results of the evaluation will be submitted to the FDA by and will focus on the following analytical tests: (b) (4) assay; SDS-PAGE gel assays; HPLC for measurement of total M6P, HPAEC-PAD for measurement of (b) (4); and SEC.

Rationale

(b) (4)

(b) (4)



4. To evaluate the use of the (b) (4) method as a release test for glycan profiling. The results of this evaluation will be submitted to the FDA by

Rationale



5. To develop an analytic method to monitor (b) (4) and to evaluate its use in the drug product release and stability specifications. Results of this evaluation together with a proposed control strategy will be submitted to the FDA by ...

Rationale



6. To evaluate the use of the (b) (4) assay and (b) (4) assay in the drug product stability program. The results of this evaluation together with a proposed control strategy will be submitted to the FDA by

Rationale

Inclusion of these assays in the stability program would provide control over critical quality attributes impacting Lumizyme efficacy that are not currently monitored by sensitive analytical methods.

7. To evaluate and revise as necessary the criterion for the system suitability requirement regarding the precision of the (b) (4). The evaluation will be submitted to the FDA by



precision of the assay, and indicate that you could tighten the acceptance criterion for assay precision to better ensure routine results are representative of the “true values”.

Executive Summary

Myozyme (rhGAA) is 110 kD, heavily glycosylated enzyme that is produced by Genzyme for Enzyme Replacement Therapy of patients with a confirmed diagnosis of Pompe's disease (a rare inherited deficiency of the enzyme acid alphasglucosidase, or GAA). In the United States Myozyme produced at a 160 L bioreactor scale is licensed for treatment of Pompe's disease in infants, while in most other countries, Myozyme produced at a 2000 L bioreactor scale is licensed for treatment of infantile and older patients. The 160 L process material was licensed by the FDA in April 2006 under BLA STN125141.

In January, 2007, Genzyme informed the Agency of a developing drug shortage due to inability to supply all US patients with the 160L product. A post licensing supplement (STN125141/75) for manufacture of Myozyme at the 2000 L scale was submitted to the FDA in November of 2007. This manufacturing supplement was also contained limited clinical data in Pompe's infants. Following FDA review, in April 2008 Genzyme was informed that the FDA considered Myozyme produced at the 160L and 2000 L scales to be two different products, and that approval of the 2000 L product would require submission of a new BLA containing clinical data demonstrating safety and efficacy, without CMC data, but rather referring to the CMC data contained in the STN125141/75 supplement. In May 2008 Genzyme submitted STN125291 (subject of this review) which contain clinical data for 2000 L product used in Late onset Pompe's patients (LOTS trial).

Although the 2000L process is the focus of this review, it is critical to discuss the relationship between the 2000L process and the 160L process because a large amount of CMC information pertinent to this product resides in the license application for the 160L process and product. Moreover, there is a priori reason to believe that a number of the product attributes for 160 L material are in the direction of greater clinical efficacy relative to 2000 L material. Thus, describing the relationships between the two processes and what additional information is necessary for the 2000L process is important to evaluate this application.

Pompe's patients are broadly divided into severely affected infants, and those with later onset disease, which is generally less severe. Classic infantile Pompe's patients have essentially complete deficiency of α -glucosidase, which causes progressive lethal degeneration of both cardiac and skeletal muscle. Without Myozyme treatment, very few infantile Pompe's disease patients live beyond their first birthday. Late-onset disease is characterized low levels of GAA, that vary from patient to patient. These reduced enzyme levels result in slowly progressing skeletal muscle weakness and degeneration, as well respiratory muscle involvement, but without cardiac effects.

Pompe's disease is treatable by enzyme replacement of GAA with recombinant GAA (rhGAA). Genzyme's licensed rhGAA product, named Myozyme, is infused into Pompe's patients, binds primarily to the (b) (4) and is transported to the lysosomes, where it can degrade glycogen inclusion bodies that build up as a result of the GAA deficiency.

Cardiac muscle in infantile Pompe's with Myozyme (at least with 160 L product) shows a relatively good response to treatment with Myozyme. However treatment of skeletal muscle is more difficult in both infantile and late-onset disease, and has also proven to be a greater challenge than substrate removal for other lysosomal storage disorders (LSDs) that have been successfully treated with ERT. Enzyme Replacement Therapy for Pompe's has proved to be challenging for a number of reasons. First, the density of the target (b) (4) receptor on muscle cells is particularly low. Moreover, there is potential for mis-targeting of the rhGAA due to uptake by the abundant mannose receptors on antigen-presenting cells, and in liver, as well as the asialoglycoprotein receptors, or ASGR, in the liver—in fact the great majority of infused rhGAA is cleared by the liver.

In addition, the high affinity ligand for the (b) (4) receptor, which mediates the major pathway for therapeutic uptake, is the (b) (4)



The important CMC issues arising from the review of this BLA are summarized as follows:

Drug Substance Process

Although the 2000L process is the focus of this review, it is critical to discuss the relationship between the 2000L process and the 160L process because a large amount of CMC information pertinent to this product resides in the license application for the 160L process and product. Thus, describing the relationships between the two processes and what additional information is necessary for the 2000L process is important to evaluate this application. Myozyme 160L product is manufactured at Genzyme's Framingham, MA facility, while the 2000 L Myozyme is produced at their Allston, MA plant. For both the 160L and the 2000 L processes, rhGAA production cells are (b) (4)

