

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125291

MICROBIOLOGY REVIEW(S)



Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue,
Building 51,
Silver Spring, MD 20993

Date: April 12, 2010
To: Administrative File, STN 125291/0/99
From: Patricia F. Hughes, Team Leader, CDER/OC/DMPQ/MAPCB/BMT *PFH 4/12/10*
Subject: Team Leader review memo of the BLA resubmission: To support 4000 L scale up of alglucosidase alfa and introduce new drug substance and drug product manufacturing sites.
US License: # 1596
Applicant: Genzyme Corporation
Mfg Facility: Drug substance: Genzyme Flanders bvba, Ciplastraat 8, 2440 Geel, Belgium (FEI number: 3003623839).
Drug Product: Genzyme Ireland Ltd, IDA Industrial Estate, Old Kilmeaden Road, Waterford, Ireland (FEI number: 3003809840).
Product: Lumizyme[®] (Alglucosidase alfa)
Dosage: 50 mg lyophilized powder for reconstitution
Indication: Treatment of non-infantile-onset patients with Pompe disease
Due Date: June 17, 2010

Recommendation for Approvability

Product Quality Microbiology:

The BLA 125291, as amended, is recommended for approval from a microbial control, sterility assurance, and microbiology product quality perspective. One Post-marketing commitment should be communicated to Genzyme in the final action letter and is as follows:

To qualify the [redacted] ^{(b) (4)} cycle for its intended use by performing an equivalency test between the D value of [redacted] ^{(b) (4)} and [redacted] ^{(b) (4)}

Final Report Submission: May 28, 2010

CGMP Acceptability of Establishments:

The manufacturing and testing facilities listed in the BLA are currently in compliance with CGMP requirements and there are no pending compliance actions that would prevent the approval of this BLA. The licensed manufacturing and testing sites include Genzyme Flanders bvba in Geel, Belgium (FEI 3003623839) for the drug substance and Genzyme

Ireland Ltd in Waterford, Ireland (FEI 3003809840) for the drug product. Alternate testing sites for the drug substance and drug product include Genzyme Corporation in Framingham, MA (FEI 1220423) and Genzyme Corporation in Allston MA (FEI 1000305672). As alternate testing sites, both laboratories have an acceptable compliance status.

The original manufacturing site, Genzyme Allston (FEI 1220423) in Allston, MA, for the 2000 L scale process was found to be unacceptable from a compliance perspective after several site inspections by New England District inspectors during the course of the review of the original BLA submission. The Genzyme Allston site was withdrawn as a drug substance and drug product manufacturing site from the BLA and the BLA was resubmitted (BLA 125291/0/99) to license the Genzyme Flanders and Genzyme Waterford facilities as product manufacturing sites.

Summary:

Alglucosidase alfa (recombinant human acid alpha-glucosidase, [rhGAA] produced in a Chinese Hamster Ovary cell line) is a hydrolase that degrades lysosomal glycogen to glucose. (b) (4)



The finished drug product is a sterile 50 mg rhGAA lyophilized powder in 20 mL Type I glass tubing vial fitted with a (b) (4) (b) (4) (b) (4) stopper and sealed with an (b) (4). The finished vial is for single use after reconstitution with 10.3 ml of sterile water for injection.

The rhGAA manufactured at 160 L scale (Myozyme[®]) was approved for the treatment of Pompe disease on April 28, 2006 (BLA STN 125141/0). Information relating to chemistry, manufacturing and controls of the 2000 L scale (Lumizyme[®]) manufacturing process was incorporated into BLA 125291 by cross-reference to BLA STN 125141/0 and BLA STN 125141/65 due to lack of comparability between 160 L and 2000 L scales. BLA 125291 received a complete response letter due to CGMP deficiencies at the Genzyme Allston manufacturing site.

A complete response resubmission to BLA 125291 was submitted on 12/16/2009 (BLA 125291/0/99; eCTD sequence number 0098). Additional amendments to the resubmission were submitted (eCTD sequence numbers: 106 dated 1/27/2010, 110 dated 3/9/2010, and 114 dated 3/19/2010) to provide clarification or additional data and information. The requests were as follows:



- Submission of summary shipping data.
- Revision of the Environmental Analysis, if needed.

Only one issue resulted in a PMC which requests that the sponsor conduct a study to verify that biological indicator (b) (4) have equivalent D-values as (b) (4). Biological indicators are used in the validation of a (b) (4) process.

Conclusions:

- I. The BLA, as amended is recommended for approval from a microbiology product quality perspective. One PMC was communicated to the firm:

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). The final study report will be submitted by May 28, 2010.

- II. Information and data in the CMC sections of the BLA not related to microbiology product quality were assessed by OBP/DTP reviewers in a separate reviews.
- III. The Genzyme Flanders drug substance manufacturing facility in Geel, Belgium was inspected by a team of CDER investigators from September 21-29, 2009 in support of treatment IND#10780 and for BLA 125291. The inspection was classified as VAI and the site has an acceptable compliance status.

The Genzyme fill/ finish facility in Waterford, Ireland was inspected October 21-30, 2009 by a CDER inspector in support of treatment IND#10780 and BLA 125291.0.99. The inspection was classified as VAI and the site has an acceptable compliance status.

STN:125291/0/99 Genzyme Corporation

CC:

Building 22, Ishihara Richard

DMPQ/BMT/Building 51, eCTD Files (STN: 125291)

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Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue,
Building 51,
Silver Spring, MD 20993

Date: April 8, 2010
To: Administrative File, STN 125291/0/99
From: Kalavati Suvarna, Ph.D., CDER/OC/DMPQ/MAPCB/BMT *ks 4/8/2010*
Endorsement: Patricia F. Hughes, Team Leader, CDER/OC/DMPQ/MAPCB/BMT *PFH 4/8/2010*
Subject: Review memo: BLA resubmission: To support 4000 L scale up of
alglucosidase alfa and introduce new drug substance and drug product
manufacturing sites.
US License: # 1596
Applicant: Genzyme Corporation
Mfg Facility: Drug substance: Genzyme Flanders bvba, Ciplastraat 8, 2440 Geel,
Belgium (FEI number: 3003623839).
Drug Product: Genzyme Ireland Ltd, IDA Industrial Estate, Old Kilmeaden
Road, Waterford, Ireland (FEI number: 3003809840).
Product: Lumizyme[®] (Alglucosidase alfa)
Dosage: 50 mg lyophilized powder for reconstitution
Indication: Treatment of non-infantile-onset patients with Pompe disease
Due Date: June 17, 2010

Recommendation for Approvability: The BLA, as amended, is recommended for approval from a microbial control, sterility assurance, and ^{(b) (4)} perspective with the following post-marketing commitment.

Post-marketing commitment 1: To qualify the ^{(b) (4)} for its intended use by performing an equivalency test between the I ^{(b) (4)} value of ^{(b) (4)} and ^{(b) (4)}. The final study report will be submitted by May 28, 2010.

SUMMARY: Alglucosidase alfa (recombinant human acid alpha-glucosidase, [rhGAA] produced in a Chinese hamster ovary cell line) is a hydrolase that degrades lysosomal glycogen to glucose. The rhGAA-manufactured at 160 L scale (Myozyme[®]) was approved for the treatment of Pompe disease on April 28, 2006 (BLA STN 125141/0). Information relating to chemistry, manufacturing and controls of the 2000 L scale (Lumizyme[®]) manufacturing process was incorporated into BLA 125291 by cross-reference to BLA STN 125141/0 and BLA STN 125141/65 due to lack of comparability between 160 L and 2000 L scales. BLA 125291 received a complete response letter due to CGMP deficiencies. This review includes assessment of the complete response resubmission to BLA 125291 (BLA 125291/0/99; eCTD sequence number 0098 dated 12/16/2009) which

contains information relating to the chemistry, manufacturing and controls of the 4000 L scale (Lumizyme[®]) manufacturing process and amendments to the submission (eCTD sequence numbers: 106 dated 1/27/2010, 110 dated 3/9/2010, and 114 dated 3/19/2010).

ASSESSMENT:

3.2. S DRUG SUBSTANCE

3.2. S.2 MANUFACTURE

3.2. S.2.1 MANUFACTURER(S):

The locations that manufacture and test the 4000 L scale rhGAA drug substance are shown below:

Drug substance manufacturing, formulation, and QC testing site:

Genzyme Flanders bvba
Cipalstraat 8
2440 Geel
Belgium
FEI number: 3003623839

Alternate QC testing sites for drug substance:

Genzyme Corporation
45 & 76 New York Avenue
Framingham, MA 01701
United States
FEI number: 1220423

Genzyme Corporation
500 Soldiers Field Road
Allston, MA 02134
United States
FEI number: 1000305672

Review comment: Genzyme Flanders site was inspected by a team of investigators led by Dr. Patricia Hughes (9-21-2009 to 9-29-2009) in support of a treatment IND#10780 for the 4000 L rhGAA product. Please see attached FDA form 483 for observations made during that inspection.

3.2.S.2.2 DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS

(b) (4)



cGMP STATUS:

There are no pending or ongoing compliance actions to prevent approval of STN 125291/0/99 at this time. The status of the manufacturing sites as of 4/8/2010 is shown below:

Establishment	FEI	Inspection date	Classification	Profile
Genzyme Flanders bvba Cipalstraat 8 2440 Geel Belgium	3003623839	September 21-29, 2009	VAI	TRP
Genzyme Ireland Ltd IDA Industrial Estate Old Kilmeaden Road Waterford, Ireland	3003809840	October 21-30, 2009	VAI	BTP, SVS, SVL
Genzyme Corporation 45 & 76 New York Avenue Framingham, MA 01701 United States	1220423	November 19 - December 5, 2008	VAI	CTX
Genzyme Corporation 500 Soldiers Field Road Allston, MA 02134 United States	1000305672	October 6-13, 2009	OAI	Acceptable for QC testing
(b) (4)	(b) (4)	(b) (4)	NAI	CTL

CONCLUSION:

- I. Sections 3.2.S and 3.2.P of the BLA pertaining to microbial control of the drug substance manufacturing process and sterility assurance information and data on the drug product manufacturing process were reviewed. The BLA, as amended, is recommended for approval from a microbial control, sterility assurance, and microbiology product quality perspective with the following post-marketing commitment.

Post-marketing commitment 1: To qualify the (b) (4) for its intended use by performing an equivalency test between the D value of (b) (4) and (b) (4). The final study report will be submitted by May 28, 2010.

- II. CMC product specific information and data should be reviewed by OBP/DTP.
- III. The Genzyme Flanders drug substance manufacturing facility in Geel, Belgium was inspected by a team of investigators led by Dr. Patricia Hughes from September 21-29, 2009 in support of treatment IND#10780 for the 4000L rhGAA product (product proposed in STN 125291/0/99). A FDA form 483 was issued to the firm. The inspection was classified as VAI.

The Genzyme fill/ finish facility in Waterford, Ireland was inspected October 21-30, 2009 by Mr. Douglas Campbell in support of treatment IND#10780 for the 4000L rhGAA product (product proposed in STN 125291/0/99). A FDA form 483 was issued to the firm. The inspection was classified as VAI.

CC: DMPQ/BMT/Building 51, Suvarna
DMPQ/BMT/Building 51, Hughes
HFD-123, Ishihara Richard
DMPQ/BMT/Building 51, eCTD Files (STN:125291)

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Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue,
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Date: January 9, 2009
To: Administrative File, STN 125291/0
From: Kalavati Suvarna, Ph.D., CDER/OC/DMPQ/MAPCB/BMT
Endorsement: Cruz Concepcion, Acting Branch Chief, CDER/OC/DMPQ/MAPCB
Subject: Review memo: New BLA for the treatment of non-infantile onset patients with Pompe disease.
US License: # 1596
Applicant: Genzyme Corporation
Mfg Facility: Genzyme Corporation, 500 Soldiers Field Road, Allston, MA 02134.
Product: Lumizyme (Alglucosidase alfa)
Dosage: 50 mg lyophilized powder for reconstitution
Indication: Treatment of non-infantile-onset patients with Pompe disease
Due Date: 29 February 2009

Recommendation for Approvability: The BLA, as amended, is recommended for approval from a microbial control, sterility assurance, and microbiology product quality perspective. A separate evaluation of the establishment will be conducted by the Case Management Team in the Office of Compliance. Approvability based on establishment acceptability will be made by the Case Management Team in the Office of Compliance.

SUMMARY: Alglucosidase alfa (recombinant human acid alpha-glucosidase, [rhGAA] produced in a Chinese hamster ovary cell line) is a hydrolase that degrades lysosomal glycogen to glucose. The rhGAA manufactured at 160 L scale was approved for the treatment of Pompe disease on April 28, 2006 (BLA STN 125141/0). The 2000 L scale manufacturing process was withdrawn from BLA STN 125141 due to inability of the applicant to show comparability of the 160 L (Myozyme) and 2000 L (Lumizyme) products. The BLA 125291/0 was submitted in eCTD format. The BLA submission contains only drug substance and drug product specifications, and justifications for these specifications. Information relating to chemistry, manufacturing and controls of the 2000 L scale manufacturing process has been incorporated into this BLA by cross-reference to BLA STN 125141/0 and BLA STN 125141/65. BLA STN 125141/0 has been reviewed previously (CMC microbiology review dated 09-28-05 by Michelle Clark-Stuart and Jianming Li) and is only summarized in the different sections of the review. Information included in BLA STN 125141/65 is reviewed here along with new information submitted to BLA 125291/0. The applicant submitted three amendments (eCTD sequence

number 022 dated 09-26-08; eCTD sequence number 037 dated 11-07-08; and eCTD sequence number 043 dated 12-11-08) to update the sterility information in section 3.2.P.3.5 of the BLA and include additional information pertaining to endotoxin specification, media fills, and bioburden specifications and monitoring. These amendments (eCTD sequence numbers 022, 037, and 043) are also reviewed here.

ASSESSMENT:

3.2. S DRUG SUBSTANCE

3.2. S.2 MANUFACTURE

3.2. S.2.1 MANUFACTURER(S)

The manufacturing sites for the drug substance listed in this section of BLA 125141/0 are as follows:

- Genzyme Corporation, 45 New York Avenue, Framingham, MA 01701.
FEI no: 1220423
 - Cell bank preparation and storage
 - QC testing

- Genzyme Corporation, 51 New York Avenue, Framingham, MA 01701.
FEI no: 1220423
 - Cell bank preparation and storage

- Genzyme Corporation, 80 New York Avenue, Framingham, MA 01701.
FEI no: 1220423
 - Backup cell bank
 - Finished product storage and distribution

- Genzyme Corporation, 74 New York Avenue, Framingham, MA 01701.
FEI no: 1220423
 - Buffer, and in-process intermediate storage

- Genzyme Corporation, 76 New York Avenue, Framingham, MA 01701.
FEI no: 1220423
 - QC testing

- Genzyme Corporation, 500 Soldiers Field Road, Allston, MA 02134.
FEI no: 1000305672
 - Cell bank preparation and storage
 - Backup cell bank
 - Buffer and in-process intermediate storage
 - Cell culture, purification, formulation, fill/finish
 - QC testing

- [REDACTED] (b) (4)
 - Mycoplasma testing

- [REDACTED] (b) (4)
 - *In-vitro* Virus Testing

3.2.S.2.2 DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS

The manufacturing process and controls for 2000 L rhGAA drug substance is fully described in section 3.2.S.2.2, BLA 125141/0 and was reviewed earlier (please see review dated 09-28-05 by Michelle Clark-Stuart and Jianming Li). The manufacturing process consists of cell culture and purification. There are no changes to the cell culture process or in-process parameter controls.

[REDACTED] (b) (4)

Satisfactory

3.2. A. APPENDICES:

3.2. A.1. FACILITIES AND EQUIPMENT:

This section is same as the original BLA 125141/0 and is not reviewed here. Please see review of original BLA 125141/0 dated 09-28-05 by Michelle Clark-Stuart and Jianming Li for additional details. The site was inspected by a team of investigators led by Ms. Debra Emerson from September 15, 2008 to October 10, 2008. A FDA form 483 was issued to the firm and contained significant cGMP deficiencies.

Environmental Assessment

Genzyme is claiming a categorical exclusion from the requirement to file an Environmental Assessment per 21 CFR 25.31(c) as (a) alglucosidase alfa is a recombinant version of a naturally occurring human substance with same metabolites and degradation products as the non-recombinant version and (b) the concentration or distribution of the substance itself entering aquatic environment is less than 1 part per billion.

cGMP Status

The cGMP assessments of the manufacturing facilities are under review by the Case Management Team in the Office of Compliance and a final decision is pending.

Conclusion

- I. Sections 3.2.S and 3.2.P of the BLA pertaining to microbial control of the drug substance manufacturing process and sterility assurance information and data on the drug product manufacturing process were reviewed. The BLA, as amended, is recommended for approval from a CMC product quality microbiology perspective.
- II. CMC product specific information and data should be reviewed by OBP/DTP reviewer.

- III. A separate evaluation of the establishment will be conducted by the Case Management Team in the Office of Compliance. Approvability based on establishment acceptability will be made by the Case Management Team in the Office of Compliance.

CC: DMPQ/BMT/Building 51, Suvarna
DMPQ/BMT/Building 51, Cruz
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HFD-123, Mills Fredrick
HFD-123, Ishihara Richard
DMPQ/BMT/Building 51, Blue Files (STN:125291)

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