CENTER FOR DRUG EVALUATION AND RESEARCH AND CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

APPLICATION NUMBER:

125141/0

CHEMISTRY REVIEW(S)

Memo

Date: December 19, 2005
Revised: April 26, 2006

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

To: Gibbes Johnson, Lab Chief, Laboratory of Chemistry, DTP, OBR, CDER
Barry Cherney, Deputy Director, DTP, OBR, CDER, Amy Rosenberg, Director DTP, OBR, CDER

Subject : Genzyme's STN 125141/0licensing application for rhGAA (Myozyme) for treatment of Pompe's disease
Review of CM & C Drug Substance Section in original BLA submission STN 125141/0/0

Executive Summary

General Background

This BLA is for the use of Myozyme (rhGAA) —— —— Pompe disease (acid alphaglucosidase 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 and finally to destruction of muscle tissue.

Myozyme (rhGAA) is an enzyme that cleaves glycogen at 1,4 glycosidic bonds, as well as to some extent, 1, 6 glycosidic bonds. Myozyme is produced by Genzyme in CHO (Chinese Hamster Ovary) cells by recombinant DNA technology. The enzyme is manufactured in bioreactors at 160 L and 2000L scales

This reviews covers Drug Substance information in the original BLA submission, designated STN 125141/0/0, which was submitted July 31, 2006. It is noteworthy that this submission contains considerable information about Myozyme manufactured at the 2,000 L scale, which has been withdrawn. This information has been reviewed, but there have been no action items for the 2,000 L process due to its withdrawal. A separate review drafted April 21, 2006 and revised in final form April 26, 2006 covers primarily the additional potency assays first described in a major amendment submitted December 31, 2005 (STN 125141/0/8), and post marketing commitments for their implementation. It is

This review is organized both in the Executive Summary and in the body of the review according to the eCTD headings for Drug Substance Manufacturing, with eCTD headings in **boldface**

Nomenclature
Trade Name- Myozyme; USAN name-alglucosidase alpha, Genzyme laboratory code – rhGAA

Structure

description is adequate

General Properties
Enzyme activity, uptake into cell and lysosomes adequately described. Review supplemented with information from literature.

Manufacturer
Adequate description in tabulated form is provided.

Description of Manufacturing Process and Process Controls
A satisfactory description of the Cell Culture and Purification processes, controls, and batch numbering at both scales is provided.

Control of Materials
A satisfactory description is provided for materials used in production, as well as

apparatus.

Control of Critical Steps and Intermediates
An adequate description of in-process controls and hold is provided.

Process Validation
A thorough description of Process Validation for the 160 L and 2000 L scales is provided. This included the lineage of lots and rationale for qualifying process steps.

Manufacturing Process Development
An adequate description is provided for Manufacturing Process Development extending from the 30/60L to 160 L scale, and then to the 2000 L scale. This section focuses primarily on comparability between scales. There is considerable overlap between this section and the section that follows immediately on Elucidation of Structure.
There a substantial number of comments on this section, which focus on 160/ 200 L comparability. It is Genzyme's view that these characterizations demonstrate

comparability between the 160 l and 2000 L material. However, examination of the data does reveal a number of differences: **These will be addressed in review of a future post-approavl supplement for the 2,000 L process.**

Elucidation of Structure
This section contains the characterization data for 3 PV lots at the 160 L scale, and 4 PV lots at the 2000 L scale. Overall, full and an adequate characterization data has been supplied. Additional data will be acquired using new assays that Genzyme has developed to be implemented post-marketing. **Issues of 160 L vs. 2,000 L structural comparablIity will be addressed in review of a future post-approval supplement for the 2,000 L process.**

Impurities
Satisfactory descriptions and rationales for the impurity tests are provided.

Specification
The Requests from the November 18, 2005 IR letter regarding modification of Lot Release Specifications are noted; i.e (preserving the IR letter numbering)
Genzyme must
35. Implement a potency assay which reflects — mannose-6-phosphate receptor and delivery to lysosomes. This assay must be used for Drug Substance and Product lot release and in stability specifications. Include data supporting the proposed acceptance criteria.
36. An — potency assay using a more physiologically relevant substrate must be implemented for Drug Substance and Product lot release and stability specifications. Include data supporting the proposed acceptance criteria. In addition, you should evaluate the feasibility of using a substrate concentration near the K_M.

37. The position and amount of — per mole of rhGAA needs to be controlled and specified. A subset of molecules containing — may be responsible for the in vivo bioactivity. Provide a specification for the position and amount of — per mole of rhGAA in Drug Substance and include data supporting the proposed acceptance criteria.
38. Establish a quantitative measurement of the — — 2st method used for Drug Substance release testing. Include data supporting the proposed acceptance criteria.
51. Tighten the limits for — in accord with manufacturing and clinical experience. Provide justification for the new limits.
52. Set a quantitative specification for the — present in oligosaccharide mapping analysis. Provide data supporting the proposed changes.
53. Include a specification for — the Drug Substance.
54. Establish a limit for the amount of — n Drug Substance.
57.

The above issues have been resolved in Amendment 8 to the BLA, and in subsequent communications between Genzyme and the FDA. The resolution of these issues is described in the separate review by Frederick C. Mills, which was finalized on April 26, 2006, or in the case of #57, in the Drug Product review by Ralph Bernstein.

Analytical Procedures –reviewed by Dr. Nikolai Spiridonov
Validation of Analytical Procedures-reviewed by Dr. Nikolai Spiridonov

Batch Analysis
A tabulation of all the 30/60 L, 160 L and 2000 L batches cited in the BLA is provided, as well as information on how the material was used, and release test data for these batches. As expected, all the batches were within specification.

Justification of Specification
The justification of existing specifications is generally adequate. However referring to several Requests from the Nov. 18, 2005 IR letter:

Request 57
— specifications in lot release and stability programs are excessively broad and must be tightened in accord with manufacturing and clinical history. Propose revised limits and justification for these limits.
There is an overriding concern that — may pose a safety problem, vis a vis immunogenicity.

Request 38
It was requested that Genzyme establish a quantitative measurement of the —
— test method used for Drug Substance release testing.
Include data supporting the proposed acceptance criteria.

Request 51
Genzyme should tighten the limits for — in accord with manufacturing and clinical experience. Provide justification for the new limits
This will be subject to negotiation, and may require using a range of less than —
However, tight control over — is important for clearance.

Request 52
Genzyme should set a quantitative specification for the — present in oligosaccharide mapping analysis. Provide data supporting the proposed changes.
Examination of the — for released oligosaccharide mapping (Manufacturing Development section) suggest they should be amenable to quantitation.
As discussed above, these issues have been addressed by Genzyme and their resolution is described in separate reviews.

Reference Standards

Genzyme SOP (QC-052-07) defines the preparation, testing and storage requirements that must be met to establish the primary reference standard. Adequate provision for creation , storage and tracking of the reference standard. Only a single reference standard at any one time is permitted. Shown are the tests for the reference standard, from QC-052-07
The reference standard will need to be re-qualified, or a new Reference Standard produced, that has been analyzed using the tests requested in the November 18, 2005 IR letter. **This issue has been addressed by Genzyme and its resolution is described in a separate review.**

Container Closure System
The descriptions of the Drug Substance container closures are satisfactory, and in agreement with what was observed during the pre-licensing inspection. The stability studies support these container closure systems, and this should be strengthened by new stability studies utilizing a new potency assay, as well as
, assays. From information on is contained in the Control of Materials section there appear to be no safety issues regarding

Stability Summary and Conclusions
appear generous, and may have an effect on long term safety. The stability limits have been set at even though the experience at the recommended storage temperature is . During the proposed storage time (see Stability Data, below)

Genzyme should commit to repeating the Drug Substance stability studies, once a new, physiologically relevant potency assay has been validated, and also include assays for in the tests.

During the Oct 24-Nov 4 pre-licensing inspection, Genzyme stated that photostability studies had been planned, but not executed. In the November 18, 2005 IR letter from the Agency, it was requested that photostability studies be performed as a condition for approval.
The above issues have been resolved in Amendment 8 to the BLA, and in subsequent communications between Genzyme and the FDA. The resolution of these issues is described in the separate review by Frederick C. Mills, which was finalized on April 26, 2006, or in the case of #57, in the Drug Product review by Ralph Bernstein

Post-approval Stability Protocol and Stability Commitment
As stated above Genzyme should commit to repeating the Drug Substance stability studies, once a new, physiologically relevant potency assay has been validated, and also include assays for in the tests.
This issue has been addressed by Genzyme and its resolution is described in a separate review.

Stability Data

The data support the proposed — hold time, with no significant changes in test parameters during this time interval.
The · — specification should be lowered.
This issue has been addressed by Genzyme and its resolution is described in a separate review.

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Review Cover Sheet

BLA STN 125141

MYOZYME® (Alglucosidase Alfa)

Genzyme

Division of Therapeutic Proteins
Frederick C. Mills, Ph.D. HFD-122
Ralph M. Bernstein, Ph.D. HFD-122
Jin Hai Wang, Ph.D. HFD-122
Ingrid Markovic, Ph.D. HFD-122
Nikolay Spiridonov, Ph.D. HFD-122
Edward Max, MD, Ph.D. HFD-122

CMC Review Data Sheet

1. **BLA#** STN 125141/0

2. **REVIEW #:** 1

3. **REVIEW DATE:** April 25,2006

4. **REVIEWERS:** Frederick C. Mills, Ph.D.
Ralph Bernstein, Ph.D.
Jin Hai Wang, Ph.D.
Ingrid Markovic, Ph.D.
Nikolai Spiridonov, Ph.D.
Edward Max, MD, Ph.D.

5. **COMMUNICATIONS AND PREVIOUS DOCUMENTS[1]:**

Previous Documents	Document Date[2]
Pre-BLA Meeting	May 3, 2005
Agency IR	November 18, 2005
Agency teleconference with Genzyme to discuss 11-18-05 IR	December 2, 2005
DTP FAX to discuss qualified assays	January 27, 2006
DTP meeting with Genzyme to discuss qualified assays	February 1, 2006
Genzyme FAX regarding qualified assays	February 7, 2006
Genzyme secure email to DTP describing qualified assay optimization	February 28, 2006
DTP teleconference with Genzyme to discuss use of qualified assays for evaluation of clinical lots	March 6, 2006
Genzyme secure email to DTP containing evaluation of clinical lots with qualified assays	March 24, 2006
DTP teleconference with Genzyme to discuss qualified assay specfications	March 31, 2006
Genzyme secure email to DTP with draft PMCs	April 6, 2006
DTP teleconference with Genzyme to discuss PMCs	April 7, 2006

DTP secure email to Genzyme with draft PMCs	April 7, 2006
Genzyme secure email to DTP with draft PMCs	April 14, 2006
DTP teleconference with Genzyme to discuss PMCs	April 14, 2006
DTP secure email to Genzyme with draft PMCs	April 20, 2006
DTP secure email to Genzyme to with draft PMCs	April 21, 2006

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	**Document Date by Desk Copy**	**Document Date to EDR**
STN 125141/0 Original Submission		July 31, 2005
STN 125141/0/06 Response to 10-26-05 and 10-27-05 drug product IR teleconference		December 13, 2006
STN 125141/0/08 Response to November 18, 2006 Agency IR		December 31, 2005
STN 125141/0/10 Responses to immunogenicity questions in November 18, 2006 Agency IR , responses to drug product questions		January 13, 2006
STN 125141/0/12 copy of 1-27-06 DTP FAX, Genzyme responses to 2-106 and 2-2-06 meetings		February 22, 2006
STN 125141/0/14 antibody titers as per 3-23-06 DTP teleconference		March 28, 2006
STN 125141/0/15 Qualified assay data for 160 L clinical lots		March 29, 2006
STN 125141/0/17 patient IgE responses		April 12, 2006

7. **NAME & ADDRESS OF APPLICANT:**

Name: Genzyme Corporation

Address: Genzyme Corporation
51 New York Avenue,
Framingham, MA 01701

Representative: Mark Hayes, Ph.D., VP Regulatory Affairs
Telephone: 508-217-3961

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: MYOZYME®
b) Non-Proprietary Name: Alglucosidase alfa
c) Code name:
d) Common name: rhGAA
e) Drug Review Status: Accelerated Review
f) Chemical Type: recombinant form of human α-glucosidase

9. PHARMACOL. CATEGORY: human α-glucosidase (maltase)

10. DOSAGE FORM: Sterile lyophilized powder.

11. STRENGTH/POTENCY:

(i) A vial of MYOZYME® (alglucosidase alfa) contains 52.5 mg product. Upon reconstitution with 10.3 ml of Sterile Water for Injection, the total extractable dose per vial is 50 mg per 10 ml

(ii) Potency of Alglucosidase alfa is assessed by hydrolysis of the synthetic substrate — — and is expressed as units/ mg. Alglucosidase alfa has a specific activity of 3 to 5 U/mg, where one unit is defined as that amount of activity that results in the hydrolysis of 1 μmole of synthetic substrate per minute under the specified assay conditions. Mass units are used for dosing.

(iii) Dating period for finished drug product is 24 months when stored at 2°C -8°C. The reconstituted and diluted solution is stable for up to 24 hours at 2° to 8°C).

12. ROUTE OF ADMINISTRATION:

MYOZYME® is to be administered intravenously, and should be diluted in 0.9% Sodium Chloride for Injection, USP, immediately after reconstitution, to a final MYOZYME concentration of 0.5 to 4 mg/mL.

13. ANIMAL- AND HUMAN-DERIVED RAW MATERIALS

The animal- and human-derived raw materials used in the manufacturing process of MYOZYME®are used in the production of the master/working cell banks and fermentation.

Item	Fetal Bovine Serum
Vendor	
Source	
Adventitious Agent Control	

Item	Donor Bovine serum
Vendor	
Source	
Adventitious Agent Control	

Item	Porcine Trypsin/EDTA
Vendor	
Source	
Adventitious Agent Control	

Item	2-deoxy cytidine
Vendor	
Source	
Adventitiou Agent Control	

Item	protamine sulfate
Vendor	
Source	
Adventitious Agent Control	

14. MYOZYME® MOLECULAR WEIGHT, DISULFIDE BONDS, GLYCOSYLATION, AND PROCESSING FORMS

MYOZYME® (alglucosidase alfa) consists of the human enzyme acid α-glucosidase (GAA), encoded by the most predominant of nine observed haplotypes of this gene. Alglucosidase alfa degrades glycogen by catalyzing the hydrolysis of α-1,4- and α-1,6- glycosidic linkages of lysosomal glycogen.

MYOZYME® ——, with a calculated mass of 99,377 daltons for the polypeptide chain.

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___ § 552(b)(4) Draft Labeling

15. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	COMMENTS
/	1	/	/	2	acceptable
	1			2	acceptable
—	1	/	/	2	acceptable

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
BB IND	/	Treatment of Pompe disease with Pharming rhGAA
BB IND	/	Treatment of Pompe disease with Synpac rhGAA
BB IND	10780	Treatment of Pompe disease with Genzyme rhGAA (MYOZYME®)

16. STATUS: The date of response and recommendation should be noted. The types of consults or related reviews that should be noted are as follows:

OBP:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Establishment Status	approval	April 21, 2006	Michelle Clark-Stuart
Labeling review on carton and vial	approval	March 31, 2006	Cristi Stark
Tradename review DMETS	MYOZYME®	February 15, 2006	Charles Hoppes,
Environmental Assessment	Categorical exclusion as per 21 CFR 25.31 (c)	March 10 2006	Michelle Clark-Stuart
TFRB	approval	April 21, 2006	Michelle Clark-Stuart

17. CMC Inspectional Activities involving product reviewers

1. Genzyme in Framingham, Massachussetts (October 24, 2005 – October 28, 2005): This facility, owned by Genzyme, is the site for manufacture of drug substance and formulated drug product. On site facilities include the manufacturing/production buildings, laboratories (Analytical Biochemistry for in-process testing, Microbiology for bioburden and sterility testing, Biologics Quality Control for drug substance and drug product release and annual GMP stability testing, Quality Control Chemistry for raw materials qualification) storage and shipping facilities. The algucosidase alfa manufacturing buildings are dedicated to biologics. Product reviewers Frederick C. Mills and Ennan Guan (trainee) along with TFRB Inspectors Michelle Y. Clark-Stuart and Jianming Li participated in this inspection. No significant deficiencies in cGMPs were identified and no FDA 483 was issued. The facility was found to be in compliance with cGMPs and capable of manufacturing alglucosidase alfa drug substance in a consistent manner.

2. Genzyme in Allston, Massachussetts (October 24, 2005-November 4, 2005) This facility, owned by Genzyme, is the site for final drug product manufacture. Facilities on site include those for fill, finish, labeling, and packaging. Tests for drug product at Allston include those for : —

   — Product reviewers Frederick C. Mills and Ennan Guan (trainee) along with TFRB Inspectors Michelle Y. Clark-Stuart and Jianming Li participated in this inspection. No significant deficiencies in cGMPs were identified and no FDA 483 was issued. The facility was found to be in compliance with cGMPs and capable of manufacturing alglucosidase alfa final drug product in a consistent manner.

The Chemistry Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of BLA #125141 for Algucosidase alfa, manufactured by Genzyme. The data submitted in this application support the conclusion that the manufacture of algucosidase alfa is well controlled, and leads to a product that is pure and potent. The product is free from endogenous or adventitious infectious agents in a way that meets or exceeds the parameters recommended by FDA. The conditions used in manufacturing have been validated, and a consistent product is produced from different production runs. It is recommended that this product be approved for human use (under conditions specified in the package insert).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

We propose the following post-marketing commitments:

1. Regarding method validations:
   a. To complete validation of — Content and — , test methods for drug substance and/or product release. Results and proposed specifications will be submitted to FDA by December 31, 2006.
   b. To complete optimization and validation of — — test methods for drug substance and product release. Results and proposed specifications will be submitted by March 31, 2007.
   c. To improve the — , content assay, or to develop, validate, and implement an alternative more accurate and precise assay. Results and proposed specification will be submitted by December 31, 2007.

2. To provide a revised protocol for requalification and confirmation of stability of the primary and working reference standards that incorporates the new panel of validated methods. A revised protocol will be submitted by July 31, 2006.
3. Regarding drug substance specifications:

a. To re-evaluate the specification for — and establish a limit for — in the specification, following assay re-validation. Results and revised specifications will be submitted by December 31, 2006.
b. To revise the specification for the — present in the oligosaccharide mapping analysis and submit by June 30, 2006.

4. Regarding the drug product COA specifications:
   a. To add the — The proposed specification will be submitted by March 31, 2007.
   b. To explore development of a method for an — observed in reconstituted drug product and after dilution in saline. Results and a proposal for controlling particle content will be submitted by November 30, 2007.

5. To characterize the composition of the — material observed after reconstitution of drug product and to investigate the nature of particle formation. Results will be submitted by November 30, 2007.

6. — validated stability indicating assays will be incorporated into the stability program (including accelerated stability on drug product, and after reconstitution and dilution). Results and revised stability protocol will be submitted by June 30, 2007.

7. To perform a study on formulated bulk drug product to confirm its hold time using the — content assay and other stability-indicating assays. Results will be submitted by November 30, 2007.

8. To conduct bracketed, in use photostability studies on product diluted for infusion using current methods. Results will be submitted by December 31, 2006.

9. To provide interim summary reports regarding progress of CMC PMCs every 6 months after licensure.

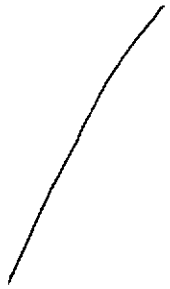
10. To provide results using the validated inhibition of enzyme uptake into human fibroblast assay from all antibody positive patients in Studies AGLU01602 and AGLU01702, as well as all patients in clinical studies or the expanded access program for Myozyme who have become invasively ventilated since February 2, 2006. Results will be submitted by October 31, 2006

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

- General: Alglucosidase alfa is the USAN name for Genzyme's MYOZYME® product. The common name is rhGAA. MYOZYME® consists of the human enzyme acid α-glucosidase (GAA), or maltase, encoded by the most predominant of nine observed haplotypes of GAA gene. MYOZYME® is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) cell line. The rhGAA molecule has [redacted] with a calculated mass of 99,377 daltons for the polypeptide chain.

- Complexity:



- Biological activity:
  Pompe's disease is a rare inherited disorder caused by a deficiency of acid alpha-glucosidase (maltase), which degrades lysosomal glycogen. This deficiency leads to accumulation of glycogen and finally to destruction of muscle tissue. The therapeutic acitivty of rhGAA results from its ability to be taken up into the lysosomes of muscle cells, and degrade the lysosomal glycogen deposits in Pompe's disease patients.

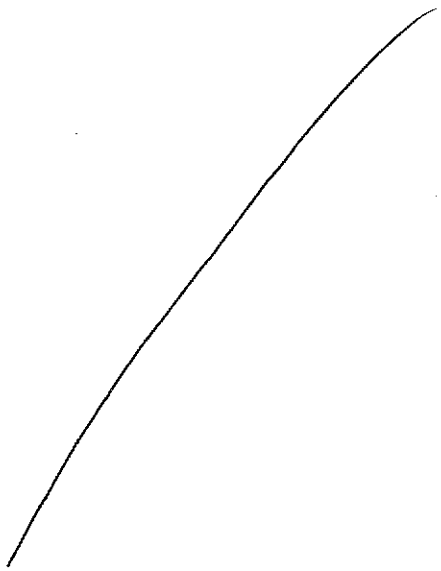
  In order to be transported to lysosomes, rhGAA first binds to mannose-6-phosphate receptors on the cell surface, [redacted] This binding is largely mediated by the [redacted]

Following receptor binding, rhGAA is taken up into the cell and transported to lysosomes. In the lysosomes, rhGAA undergoes a defined series of proteolytic and glycolytic processing steps, resulting in enzyme species with 7-10 fold increased affinities for glycogen relative to unprocessed rhGAA. These species hydrolyze glycogen, resulting in removal of glycogen deposits from the lysosomes.

- Potency Assays to Measure Activity.

  The potency of MYOZYME® is currently defined for lot release by hydrolysis of the synthetic substrate , and is expressed as units/ mg rhGAA. This substrate Unit activity is defined as that amount of activity that results in the hydrolysis of 1 µmole per minute under the specified assay conditions. This substrate , and thus is unlikely to be sensitive to changes in enzyme structure. Furthermore this assay supplies no information about binding of rhGAA to mannose-6-phosphate receptors, and cellular uptake and processing by lysosomes.

  For these reasons, at the FDA's request Genzyme developed five additional assays that capture the important activities of rhGAA. These assays are:



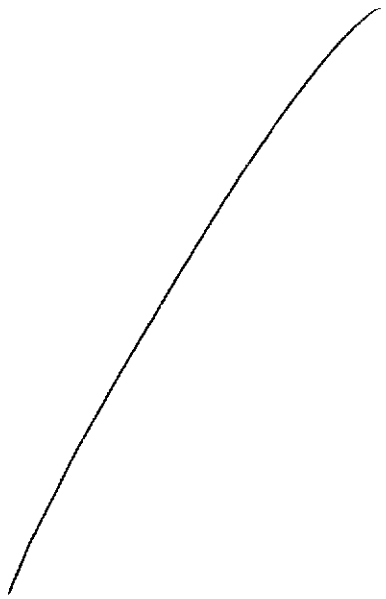
These assays are not fully validated at the present time, but are being used with specifications agreed upon between Genzyme and the FDA. As part of

their post-marketing commitments, Genzyme has agreed to validate these assays and use them for MYOZYME® lot release.

- Drug Product Presentation: MYOZYME®is supplied as a sterile, non-pyrogenic lyophile for IV infusion administration. Each vial contains 52.5 mg of Myozyme, 210 mg of mannitol, 0.5 mg of polysorbate 80, 9.9 mg of sodium phosphate dibasic heptahydrate , 31.2 mg of sodium phosphate monobasic monohydrate, — The DP is packaged in 20 cc Type glass tubing vials, stoppered with a siliconized 20 mm gray butyl — stopper and a — — aluminum seal, single-use vial free of preservatives.

- Excipients: upon reconstitution with sterile water for injection, Myozyme drug product contains (in addition to — mg/ml Myozyme). — mg/ ml polysorbate 80 — mg/ ml mannitol — mg/ ml sodium phosphate monobasic, and — mg/ ml sodium phosphate dibasic. There are no novel excipients.

- DS Manufacture



- DS Purity:

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- Degradation and Stability.

- Drug Substance: A drug substance shelf life of — is recommended based upon information submitted by the sponsor. A formulated drug product shelf life of — is recommended, based upon information submitted by the sponsor.
- Drug Product: A drug product shelf life of 24 months stored at 2-8 °C is recommended based upon information submitted by the sponsor. The Drug

product should be designated as "protect from light." The reconstituted and diluted drug product should be used within 24 hours.

Evaluation of the current assays utilized to detect potential human anti-rhGAA antibodies was performed by CMC reviewers. IgE antibody was detected in 3 out of 38 patients with infusion associated reactions among 280 treated patients with a validated ELISA. 89% (34/38) of patients in trials 1702 and 1602 tested positive for antibodies to rhGAA using the validated anti-GAA ELISA and radioimmunoprecipitation assays. Anti-GAA antibody was detected in the first three months in most patients. Patients with nonsense/frameshift mutations tended to exhibit high persistent titers of IgG antibody that was associated with more infusion associated reactions, invasive ventilation needs, loss of motor milestones and deaths. Considering the requirement for GAA to bind to cell surface mannose-6-phosphate receptors to gain entry to the cell, and to traffic to lysosomes, it is crucial to assess the ability of antibody to block such uptake and trafficking. In this regard, development of a novel -**uptake neutralization assay** was required by the immunogenicity reviewer. A PMC for validation of this assay and for the testing of sera from patients with detectable binding antibody, or sera from patients with a poor clinical response, but lacking antibody, has been established.

Because of the association of severe genetic lesions with high titer antibody responses and poor clinical outcome, a PMC was established for clinical studies for tolerance induction in the following settings:

A preventive protocol for tolerance induction that would commence with the onset of therapy

A protocol for tolerance induction in the setting of patients with ongoing immune responses.

B. Description of How the Drug Product is Intended to be Used

The recommended dosage regimen of MYOZYME is 20 mg/kg body weight administered every 2 weeks as an intravenous infusion. The total volume of infusion is determined by the patient's body weight and should be administered over approximately 4 hours.

Infusions should be administered in a step-wise manner using an infusion pump. The initial infusion rate should be no more than 1 mg/kg/hr. The infusion rate may be increased by 2 mg/kg/hr every 30 minutes, after patient tolerance to the infusion rate is established, until a maximum rate of 7 mg/kg/hr is reached. Vital signs should be obtained at the end of each step. If the patient is stable, MYOZYME may be administered at the maximum rate of 7 mg/kg/hr until the infusion is completed. The infusion rate may be slowed and/or temporarily stopped in the event of infusion reactions. Table 3

below describes the rate of infusion at each step, expressed as mL/hr based on the recommended infusion volume by patient weight.

Table 3. Recommended infusion volumes and rates

Patient Weight Range (kg)	*Total infusion volume (mL)*	*Step 1 1 mg/kg/hr (mL/hr)*	*Step 2 3 mg/kg/hr (mL/hr)*	*Step 3 5 mg/kg/hr (mL/hr)*	*Step 4 7 mg/kg/hr (mL/hr)*
1.25 - 10	*50*	*3*	*8*	*13*	*18*
10.1 – 20	*100*	*5*	*15*	*25*	*35*
20.1 – 30	*150*	*8*	*23*	*38*	*53*
30.1 – 35	*200*	*10*	*30*	*50*	*70*
35.1 – 50	*250*	*13*	*38*	*63*	*88*
50.1 – 60	*300*	*15*	*45*	*75*	*105*
60.1 – 100	*500*	*25*	*75*	*125*	*175*
100.1 - 120	*600*	*30*	*90*	*150*	*210*

- MYOZYME® is supplied as 52.5 mg/vial, sterile lyophile free of preservatives.
- MYOZYME® is prepared for IV infusion by reconstituting each vial with 10.3 mL of SWFI, for intravenous infusion.
- MYOZYME® vials should be refrigerated at 2-8 °C and protected from light. The recommended expiration dating period for MYOZYME® Drug Product is 24 months under these storage conditions.

C. Basis for Approvability or Not-Approval Recommendation

- MYOZYME® is manufactured by a robust process with precautions for contamination by cell substrate or adventitious agents. MYOZYME® is manufactured consistently, resulting in a safe and effective product, and should be approved for the proposed indication.
- Post-marketing commitments described in the recommendations section above will provide additional information to assure the continued safety of the product. The use of five qualified assays with specifications agreed by the FDA will provide additional assurance of potency and product quality. Genzyme has committed to validate these assays and use for lot release.

III. Administrative

A. Reviewers' Signature

Product Reviewer: Frederick C. Mills , Ph.D.

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A. Reviewers' Signature

Product Reviewer: Frederick C. Mills , Ph.D. Frederick C. Mills 4-27-06

Product Reviewer: Ralph Bernstein, Ph.D. Amy Rosenberg for Ralph Bernstein 4-27-06

Product Reviewer: Jin Hai Wang, M.D., Ph.D. 4-27-06

Product Reviewer: Ingrid Markovic, Ph.D. 4/27/06

Product Reviewer: Nikolay Spiridonov, Ph.D. N Spiridonov. 4.27.06.

Product Reviewer: Edward Max, MD, Ph.D. Edward Max 4-27-06

B. Endorsement Block

Product Team Leader: Gibbes Johnson, Ph.D. 4-26-06

Product Deputy Director: Barry Cherney, Ph.D. Amy Rosenberg for Barry C 4-27-06

Product Division Director: Amy Rosenberg, M.D. Amy Rosenberg 4-26-0

C. CC Block

Acting Office Director: Steven Kozlowski, MD. Signed Steve 4/27/06 for S.

Division of Therapeutic Proteins File/BLA STN 125141/0

D

736 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

genzyme

Environmental Assessment

Statement Of Exemption Under A Categorical Exclusion

In accordance with the National Environmental Policy Act; Revision of Policies and Procedures, Final Rule published in the Federal Register (62 FR 145, 7/29/97) this Biologics License Application for **Myozyme** meets the criteria for categorical exclusion under 21 CFR Section 25.31(c).

Section 25.31(c) provides for a categorical exclusion regarding an action on a BLA, for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. In the case of **Myozyme**, it is a recombinant version of a naturally occurring human substance, which would have the same metabolites or degradation products as the non-recombinant version. In addition, the concentration or distribution of the substance itself and therefore, its metabolites and degradation products would be significantly less than 1 part per billion entering the aquatic environment. The action, therefore, would not alter significantly the concentration in the environment.

To demonstrate the concentration level, the equation for the expected introduction concentration (EIC) from direct use in human beings in a given year is presented as follows:

EIC-Aquatic (ppb) = A x B x C x D where

A= kg/year produced for direct use (as active moiety)

B=1/liters per day entering POTW's (1.214×10^{11} liters per day)

C=year/365 days

D= 10^{9} ug/kg (conversion factor)

The estimated production for **Myozyme** is based on total production volume of [redacted] per year.

The calculation for EIC-aquatic (ppb) for **Myozyme** is:

[redacted] /year x 1/ 1.214×10^{11} L/day x year/365 days x 10^{9} ug/kg =

[redacted] ug/L or [redacted] ug/L or [redacted] ppb

The concentration of **Myozyme** that potentially would enter the aquatic environment would be [redacted] ppb and would therefore, not significantly alter its concentration in the environment.