

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125291

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	May 18, 2010
From	Lynne Yao, M.D., Acting Clinical Team Leader, DGP
Through	Donna J. Griebel, M.D., Director, DGP
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	BLA 125291/0/99
Supplement#	Complete Response Resubmission
Applicant	Genzyme
Date of Submission	December 16, 2009
PDUFA Goal Date	June 17, 2010
Proprietary Name / Established (USAN) names	Lumizyme/Alglucosidase alfa
Dosage forms / Strength/Dose	Intravenous injection/50 mg/10 mL vial (reconstituted)/ 20 mg/kg every other week
Proposed Indication(s)	Late-onset Pompe disease
Recommended:	<i>Approval</i>

Lynne Yao MD
5/18/10

1. Introduction

This memorandum reviews the information submitted by the Applicant, Genzyme, in response to a second Complete Response Letter issued by the Agency on November 13, 2009, for BLA 125291, Lumizyme (alglucosidase alfa, 4000 L bioreactor scale product), for the treatment of late-onset Pompe disease. This review focuses on the deficiencies cited in the second Complete Response Letter issued and the adequacy of the responses provided by the Applicant regarding these deficiencies. Both the first and second Complete Response Letters noted persistent deficiencies at the Allston Landing, MA manufacturing facility. These deficiencies were previously noted in a Warning Letter issued by the Office of Compliance on February 27, 2009. The manufacturing facilities were re-inspected in May and October, 2009, but the deficiencies were not adequately resolved and led to the second Complete Response Letter issued on November 13, 2009.

After the second Complete Response Letter was issued, discussions were held with the Applicant regarding the information that would be accepted as part of the second Complete Response submission (i.e., third review cycle). These discussions were held in the context of the persistent drug shortage of Myozyme (alglucosidase alfa produced at the 160 L bioreactor scale) for adult Pompe patients in the U.S (see section 11.C). Briefly, Myozyme was approved in 2006 for the treatment of all Pompe patients. However, the Applicant was unable to meet demand and a drug shortage developed. Lumizyme (alglucosidase alfa produced at the 2000 L and 4000 L bioreactor scale) was made available under IND through an expanded access program. The original and first complete response submissions included data for the 2000 L scale product only. However, the 2000 L product is produced exclusively at the Allston Landing, MA facility, the facility cited in the Warning Letter and in both previous Complete Response actions. Furthermore, a timeframe to adequately address the persistent manufacturing deficiencies noted at the Allston Landing, MA facility could not be determined because further compliance actions involving the facility were possible. Therefore, an

adequate Complete Response that could be submitted in a reasonable time period to address the drug shortage would likely require review of a Lumizyme product that was not produced at the Allston Landing, MA facility. Thus, the Agency and Applicant agreed that manufacturing information and product quality information already submitted by the Applicant for the 4000 L bioreactor scale product under IND 10,780 could be submitted to address the deficiencies cited in the second Complete Response Letter. The 4000 L drug substance is manufactured at the Genzyme Flanders facility in Geel, Belgium, and the 4000 L drug product is manufactured at the Genzyme facility in Waterford, Ireland. This plan would eliminate the requirement for the Allston Landing facility to hold a satisfactory compliance status as a condition of approval of Lumizyme because the Allston Landing facility is not used in the manufacture of the 4000 L Lumizyme product. Thus, in the current Complete Response submission, the Applicant has withdrawn the request for licensure of the Allston Landing facility where 2000 L product is manufactured, and is requesting licensure of the Genzyme Flanders and Waterford facilities for manufacture of the 4000 L product. However, the Agency required that the Applicant demonstrate sufficient biochemical comparability between the 2000 L and 4000 L Lumizyme products, or additional clinical information would be required. Additionally, the Applicant was required to provide clinical safety information on the 4000 L Lumizyme product from the expanded access program in the U.S., and from the post-marketing experience in Europe, where the 4000 L product was approved in February, 2009. Finally, as negotiated in previous review cycles, a Risk Evaluation and Mitigation Strategy (REMS, as described below); clinical, clinical pharmacology, and CMC post-marketing requirement and commitment studies; and revised labeling were also required as part of the second Complete Response submission. These items were included in the Applicant's second Complete Response submission and have been reviewed.

Clinical and clinical pharmacology post-marketing requirement and commitment studies were previously negotiated with the Applicant during the second review cycle. However, additional CMC post-marketing commitment studies were negotiated during the current review cycle to further characterize and validate the 4000 L production processes.

A REMS was required by the Applicant to mitigate the potential 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 for whom the safety and effectiveness of Lumizyme have not been evaluated, and to ensure that the known risks of anaphylaxis and severe allergic reactions, and the potential risks of severe cutaneous and systemic immune-mediated reactions to Lumizyme are communicated to patients and prescribers. A satisfactory REMS was negotiated with the Applicant during the current review cycle. The Lumizyme Access, Control, and Education (ACE) Program includes all components of a REMS to ensure that the benefits of Lumizyme outweigh the risk. The ACE program includes goals; a communication plan; elements to assure safe use; an implementation system; and a system of assessments. A medication guide was not required because patients would be expected to receive treatment only at specialized infusion centers under the supervision of trained personnel.

Based on a review of the information provided from each of the review disciplines, I recommend an Approval action for Lumizyme. The product quality data presented support the comparability of the 4000 L scale product to the 2000 L scale product. The overall safety and

effectiveness of the 2000 L product was demonstrated in data presented in the two previous review cycles. Thus, with the establishment of physicochemical comparability between the 4000 L and 2000 L scale products, the data support the overall safety and effectiveness of Lumizyme (4000 L scale product) in the treatment of patients 8 years of age and older with late (non-infantile) onset Pompe disease who do not have evidence of cardiac hypertrophy. However, the safe use of Lumizyme cannot be established without the implementation of a REMS. Additionally, the long-term safety and effectiveness of Lumizyme cannot be established without the recommended nonclinical, clinical pharmacology, and clinical postmarketing requirement and commitment studies.

2. Background

A. Clinical Background

Pompe disease, also known as glycogen storage disease Type II (GSD II) or acid maltase deficiency (AMD) is a rare, autosomal recessive disorder of glycogen metabolism caused by the absence or marked deficiency of the lysosomal enzyme acid- α -glucosidase (GAA). Patients with deficiency of this enzyme develop accumulation of lysosomal glycogen. This accumulation of lysosomal glycogen produces effects in various tissues, particularly in cardiac and skeletal muscle, and hepatic tissues, resulting in development of severe and progressive muscle weakness, cardiomyopathy, and impairment of respiratory function. Three clinical forms of Pompe disease are described: infantile-, juvenile- and adult-onset forms. The infantile-onset form leads to severe cardiomyopathy, muscle weakness and death usually by 18 months of age. The juvenile- and adult-onset forms are generally more attenuated, with symptoms developing in childhood or early adulthood and progressing over years to decades. In the juvenile- and adult-onset forms, known collectively as the late-onset form, deficiency of this enzyme results in the accumulation of glycogen in the lysosomes of a variety of cells, but predominantly in skeletal muscle. This accumulation of glycogen in skeletal muscle lysosomes results in progressive muscle weakness. Death in all forms is usually a result of respiratory failure. The frequency of this disease varies between ethnic groups and clinical forms. The frequency of infantile-onset appears to be highest in African-Americans 1/14,000 and Chinese 1/40-50,000. The frequency of late-onset disease is approximately 1/60,000 in Caucasian populations.¹

Alglucosidase alfa, recombinant human acid- α -glucosidase (rhGAA), is a purified analog of the naturally occurring, endogenous lysosomal GAA. The rationale for this therapy is that exogenous administration of alglucosidase alfa should theoretically replace the deficiency of endogenous enzyme in Pompe disease patients. Alglucosidase alfa is produced by recombinant DNA technology developed in a Chinese hamster ovary (CHO) cell line, and has a molecular weight of approximately 109 kD. After intravenous administration, alglucosidase alfa is internalized by cells via cellular membrane mannose-6-phosphate receptors binding to enzyme mannose-6-phosphate residues. The enzyme is then taken up by lysosomes and undergoes proteolytic cleavage resulting in increased enzymatic activity. It then exerts enzymatic activity in cleaving glycogen present in lysosomes.

¹ Scriver CR, Beaudet AL, Sly WS, et. al. The Metabolic and Molecular Bases of Inherited Disease, eighth ed., McGraw-Hill Medical Publishing, New York, 2001, pg. 3389-3420

B. Regulatory History

As noted above, the Applicant manufactures alglucosidase alfa for use in the United States (U.S.) in three production scales, a 160 L production scale (Myozyme), and a 2000 L and 4000 L production scale (Lumizyme). Currently, the only treatment approved in the U.S. for Pompe disease is Myozyme. Myozyme was approved in the U.S. based on a single clinical trial (n=18) that demonstrated improved ventilator-free survival in patients with infantile-onset Pompe disease (age \leq 7 months at the time of first infusion) as compared to an age-matched, untreated historical control. Approval of Myozyme in the U.S. for all forms of Pompe disease was based solely on this infantile-onset trial; there have been no controlled studies that have evaluated the efficacy of Myozyme in late-onset Pompe disease.

The 2000 L product was approved for use in Canada, Europe, and a number of other countries throughout the world; however, given the inability to establish product comparability based on chemistry, manufacturing and controls (CMC), pharmacokinetic, or clinical data, the 160 L and 2000 L alglucosidase alfa products were deemed to be different products by the U.S. Food and Drug Administration (FDA) in April, 2008. Therefore, the FDA required the Applicant to submit efficacy and safety data to support separate licensure of the 2000 L product.

Production of 160 L product has not been able to meet the demand for 160 L product in the U.S. and a drug shortage exists (see section 11.D). The Applicant has limited availability of the 160 L product to patients less than 18 years of age, with the 2000 L and 4000 L products available to adult patients on a case-by-case basis through an Applicant-supported expanded access program (under the IND 10,780). It should be noted that Myozyme is the tradename given to the 160 L product within the U.S., but outside the U.S., Myozyme is the tradename used for the 2000 L and 4000 L products. However, given the requirement for separate licensure of these products in the U.S., the Agency and Applicant have agreed in the U.S. to name the 160 L product, Myozyme, and the 2000 L and 4000 L products, Lumizyme.

Initial Submission

In May, 2008, Genzyme submitted a separate BLA seeking the approval of the 2000 L product because comparability with the 160 L product could not be established based on clinical, nonclinical, or biochemical data. The clinical data submitted for review included one multicenter, randomized, double-blind, placebo-controlled trial of 90 late-onset Pompe disease patients (Late-Onset Treatment Study or LOTS). Numerous statistical analysis issues were identified during the review and led to concerns regarding the Applicant's analysis of the primary endpoints; change in distance walked at 78 weeks in a six-minute walk test (6MWT), and change in % predicted forced vital capacity (% predicted FVC). An Endocrinology and Metabolic Drugs Advisory Committee (EMDAC) was convened on October 21, 2008, to obtain advice regarding statistical and clinical review issues. The committee voted 16 to 1 to approve the 2000 L product based on the clinical data presented. However, the majority of the committee recommended approval under 21 CFR 601 Subpart E, accelerated approval, based on improvement in % predicted FVC. Under Accelerated Approval regulations, the Applicant would be required to perform a post-marketing verification study to confirm the clinical effectiveness of the 2000 L product. The committee also voted 17 to 0 to require post-marketing safety studies to address the concerns of anaphylaxis, immunogenicity, and

potential chronic immune-mediated reactions. The committee members also recommended that a REMS be required to ensure the safe use of the 2000 L product.

Despite the EMDAC vote to recommend accelerated approval of the 2000 L product, the Agency was unable to approve the 2000 L product during the first review cycle because of several deficiencies including:

1. Manufacturing facility deficiencies that led to the issuance of a Warning Letter
2. Product quality (CMC) deficiencies
3. Inability to agree upon a verification study required for Subpart E approval
4. Inability to agree upon a final Risk Evaluation and Mitigation Strategy (REMS)

Thus, a Complete Response Letter was issued on February 27, 2009 by J. Beitz, Director, Office of Drug Evaluation III.

First Complete Response Submission

The Agency and the Applicant held discussions between February and May, 2009, to review the design and conduct of a verification study required for Subpart E approval. The Agency and Applicant agreed that additional information from the Pompe Registry may be sufficient to provide full approval for the 2000 L product. The Pompe Registry is a multinational disease registry with clinical outcome data collected in Pompe patients treated with since 2006. Therefore, additional clinical outcome data from the Pompe Registry submitted as part of the Applicant's complete response was believed to offer the potential for the elimination of the requirement for approval under Subpart E, and the requirement to perform a verification study. A safety update was also required as part of the Complete Response and was reviewed. Additionally, final product labeling, and the the 2000 L product REMS were negotiated during this review cycle.

The Reviewer also notes the Agency was informed by the Applicant in January 2009 that they intended to seek approval of a 4000 L product in the U.S. during the course of 2009. Genzyme received marketing approval for the 4000 L product in the European Union (EU) based on biochemical comparability in February 2009. The Applicant also informed the Agency in April 2009 that the company was not planning to continue producing the 2000 L product in the U.S. after September 2009. Despite this, Genzyme planned to submit a Complete Response to the 2000 L product application so that the 4000 L product could be later submitted as a supplement to the 2000 L product BLA, assuming a favorable outcome of the 2000 L product resubmission. Based on this scenario, the Applicant estimated that a drug shortage for the 2000 L product would be likely after September, 2009, if the 4000 L product was not approved in the U.S. Therefore, the Agency agreed to attempt to take an early action after the Applicant's submission of a complete response planned for May 2009. However, a re-inspection of the Allston Landing facility by the New England District Office in May 2009, revealed that the Applicant had not completed all the corrective actions required in the Warning Letter, and that the corrective actions would not be fully in place until September 2009. Therefore, a re-inspection of the Allston Landing facility was scheduled for early October 2009. Thus, despite efforts by the Agency to facilitate an early action to alleviate the

drug shortage issue, the Applicant was unable to institute all corrective actions to address the deficiencies cited in the Warning Letter to allow for an action on the 2000 L product resubmission before late October 2009. Furthermore, the re-inspection of the Allston landing facility in October 2009 uncovered persistent manufacturing deficiencies. The Manufacturing Assessment and Pre-Approval Compliance Branch completed its review and evaluation of the Therapeutic Biologic-Establishment Evaluation Report (TB-EER) and classified the Allston Landing, MA facility as Official Action Indicated (OAI), an unacceptable compliance status. The New England District Office determined that the facility did not comply with requirements set forth in the 21 CFR 601.20 (a) and (d). As a result of the adverse findings, NEDO updated the firm's GMP profile to "further action indicated" on November 6, 2009. Therefore, the Office of Compliance, Division of Manufacturing and Product Quality (DMPQ) issued a memo recommending a withhold approval action be taken for the 2000 L product on November 6, 2009.

Based on the unacceptable compliance status of the Allston Landing manufacturing facility for the 2000 L product, and the recommendation to withhold approval from the Office of Compliance, a Complete Response Letter was issued for the Lumizyme BLA (STN 125291) by J. Beitz, Director, Office of Drug Evaluation III, on November 13, 2009.

Current Submission

The original and first complete response submissions included data for the 2000 L scale product only. However, the 2000 L product is produced exclusively at the Allston Landing, MA facility, the facility cited in the Warning Letter and in both previous Complete Response actions. Furthermore, a timeframe to adequately address the persistent manufacturing deficiencies noted at the Allston Landing, MA facility could not be determined because further compliance actions involving the facility were possible. Therefore, an adequate Complete Response that could be submitted in a reasonable time period to address the drug shortage would likely require review of a Lumizyme product that was not produced at the Allston Landing, MA facility. Thus, the Agency informed the Applicant during a teleconference on November 20, 2009 that manufacturing information and product quality information already submitted by the Applicant for the 4000 L bioreactor scale product under IND 10,780 could be submitted to address the deficiencies cited in the second Complete Response Letter. Additionally, the Agency informed the Applicant that a safety update that included all post-marketing safety information on the 4000 L product (marketed in the EU), and safety information from patients receiving 4000 L product as part of the expanded access program within the U.S. would be required as part of the Complete Response.

The Lumizyme BLA 125291 second Complete Response resubmission was dated December 16, 2009. It was classified as a six-month resubmission with a PDUFA deadline of June 17, 2010. However, due to the persistent drug shortage, the review divisions have accelerated the review schedule and planned an early action for the current submission.

The information contained in the current submission includes the following:

1. CMC comparability information between rhGAA made at the 4000 L manufacturing scale and rhGAA made at the 160 L and 2000 L manufacturing scales

2. Nonclinical pharmacokinetic comparability assessments for the 4000 L material.
3. CMC information regarding the 4000 L drug substance manufacturing process at Genzyme Flanders in Geel, Belgium and 4000 L drug product manufacturing process at the Genzyme facility in Waterford, Ireland.
4. Clinical safety update including patients in the U.S. enrolled in the Alglucosidase Temporary Access Program (ATAP) who transitioned to the 4000 L scale product. The safety update covered a period from October 19, 2009 to November 24, 2009. Post-marketing safety data for patients outside the U.S. who were treated with the 4000 L product from December 29, 2008 through September 28, 2009.
5. A risk evaluation and mitigation strategy (REMS), product labeling, and post-marketing commitment and requirement studies.

No Advisory Committee meeting was convened to discuss this resubmission; however, an advisory committee was convened during the first cycle review as described above.

The following review disciplines have provided written evaluations and recommendations that were reviewed as part of this document:

Clinical Review by C. Mueller, dated April 7, 2010

Clinical Review by L. Yao, dated May 18, 2010

Chemistry Review (Division of Therapeutic Proteins) by J.H. Liu, and CMC Executive Summary by E. Lacana, with concurrence by B. Cherney and A. Rosenberg, dated March 25, 2010

Division of Medication Error Prevention and Analysis (DMEPA) Proprietary Name, Label and Labeling Review by Z. Oleszczuk, dated March 24, 2010

CDER Office of Compliance, Division of Manufacturing and Product Quality, Biotech Manufacturing Team (BMT) review by K. Suvarna dated April 8, 2009, with concurrence by P. Hughes, dated April 12, 2010.

The reviews should be consulted for more specific details of the application. The reader is also referred to the CDTL and primary reviews from both the original and second cycle reviews. This memorandum summarizes selected information from the review documents, with primary emphasis on the issues to be resolved in the current review cycle.

3. Chemistry, Manufacturing, and Controls

A. General product quality considerations

Alglucosidase alfa is produced as a lyophilized powder that is intended for intravenous injection. The product is provided in a 20 ml vial containing 52.2 mg alglucosidase alfa, along with various excipients. Each vial contains 50 mg of alglucosidase alfa. The drug substance and the drug product are manufactured by Genzyme Corporation (the Applicant) at the Allston Landing, MA facility.

Initial Submission

The reader is referred to the product quality review by F. Mills, dated February 27, 2009, for complete details.

During the initial review, the chemistry reviewer noted several critical product attributes that differed between the 160 L (Myozyme) and 2000 L products. These differences include a

[REDACTED] (b) (4)

These differences in critical product attributes could potentially contribute to differences in potency and immunogenicity between the two products. Additionally, the chemistry review included several deficiencies that were not addressed by the Applicant during the first review cycle and were noted in the Complete Response letter:

1. Cell viability is a critical parameter for controlling product quality during [REDACTED] (b) (4). You will need to provide adequate justification for not using cell viability as an in-process control for bioreactor monitoring.
2. An established reference standard for use in your testing control strategy that is representative of the 2000 L process has not been submitted to this BLA. You will need to provide data to support the qualification of a reference standard.
3. The acceptance criteria for drug substance and drug product specifications are not consistent with manufacturing process capability and considerations regarding potential impact on safety and efficacy. You will need to provide an evaluation on the following analytical tests: cIEF; [REDACTED] (b) (4) SDS-PAGE gel assays; HPLC for measurement of total mannose-6-phosphate (M6P); HPAEC-PAD for measurement of [REDACTED] (b) (4) and size exclusion chromatography.

[REDACTED] (b) (4)

First Complete Response submission

The reader is referred to the product quality review dated September 14, 2009, by F. Mills for complete details.

The Applicant submitted information to address all four CMC deficiencies.

1. The Applicant has proposed monitoring two cell culture metabolic parameters [REDACTED] (b) (4) in place of cell viability monitoring, and to establish in process control limits for cell viability during the [REDACTED] (b) (4) period as a post-marketing commitment.
2. The Applicant included data to support the proposed 2000 L reference standard [REDACTED] (b) (4). There appears to be consistency in critical quality attributes [REDACTED] (b) (4).

(b) (4) between (b) (4) and the 2000 L product. Additionally, (b) (4) appears to be an in-trend standard for the 2000 L product based on silver-stain SDS-PAGE and Western blot data.

3. The Applicant has provided acceptance criteria (b) (4) that have been agreed upon with the Division of Therapeutic Proteins.

4. (b) (4)

The Applicant Complete Response to the CMC deficiencies addresses all the deficiencies noted in the Complete Response Letter. Additionally, the Applicant has agreed to perform additional post-marketing commitment studies to further evaluate release testing for drug substance, release and stability specifications, drug product stability, and cell viability.

Current Submission

The reader is referred to the product quality review by J.H. Liu, for complete details.

This review will focus the product quality reviewer's evaluation of the physicochemical comparability of the 2000 L and 4000 L products and potential impact of the change in manufacturing process for the 4000 L product on critical product quality attributes.



(b) (4)

The impacts of these changes on drug substance characterization are discussed below. However, the overall validation of the purification process was assessed as adequate. Additionally, the product quality reviewer recommended the addition of a (b) (4) assay to the testing program.

Drug Substance Characterization

Overall, the proposed drug substance specifications for the 4000 L product are unchanged from the 2000 L product. (b) (4)

(b) (4)

(b) (4)

(b) (4)

Drug substance and drug product stability

Degradation studies appear to indicate that the 4000 L and 2000 L drug substances degrade in response to pH and temperature at similar rates. (b) (4)

(b) (4) However, the reviewer notes that (b) (4) is not the only degradation pathway because (b) (4) degradation studies. Additionally, stability studies of the drug product show similar attributes

between the 4000 L and 2000 L products. However, the reviewer notes that stability cannot be adequately assured using (b) (4) assays alone. Therefore, both (b) (4) assays should be included in the drug substance and drug product stability program.

Drug product comparability

There were no substantive differences in the drug product lots manufactured from the same formulated 4000 L drug substance lot at the two sites evaluated (Allston Landing, MA and Waterford, Ireland). The reviewer concluded that based on these data, the 4000 L drug product lots manufactured at the Waterford, Ireland facility are likely to be comparable to the 2000 L product manufactured at the Allston Landing, MA facility.

Final Recommendation

The data provided for review establish the physicochemical comparability between the 4000 L product and the 2000 L product. Additionally, there appear to be improvements in the 4000 L product in several attributes critical for product quality. Thus, the product quality reviewer concluded that the 2000 L and 4000 L processes manufacture materials that are highly similar and that the minor differences noted are unlikely to have clinical consequences. Furthermore, 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. Therefore, the product quality reviewer recommends approval of the 4000 L product. However, the recommendation for approval includes an agreement with the Applicant to perform 11 post-marketing commitment studies (see section 8.D). The PMC studies were negotiated to further characterize and validate the 4000 L production processes were negotiated as post-approval studies because of the current drug shortage. These studies will promote improved product quality, but were not assessed as critical to the approval of Lumizyme. The Deputy Director and Director for the Division of Therapeutic Proteins concurred with this recommendation.

B. Facilities review/inspection

Initial Submission

The Division of Manufacturing and Product Quality (DMPQ) performed a facility inspection of the Applicant's Allston Landing facility, where the 2000 L product is manufactured and this inspection uncovered several deviations from current Good Manufacturing Practices. These deficiencies were cited in an FDA Form 483 issued to the Applicant on October 10, 2008. The Applicant issued a response to these deficiencies; however, the response was deemed inadequate, and the Office of Compliance issued a Warning Letter on February 27, 2009, based on the following deficiencies:

1. Failure to establish and follow written procedures designed to prevent microbiological contamination of drug products
2. Failure to assure that there are written production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess

3. Failure to follow written procedures for the maintenance of equipment used in the manufacture, processing, packaging or holding.
4. Failure to maintain computerized systems in a validated state.

The Office of Compliance also recommended that a withhold approval action be taken.

It should also be noted that during the first review cycle, a 2000 L bioreactor crashed (i.e., rapid cell death occurred in the bioreactor) at the Allston Landing facility on November 14, 2008. In addition, a 4000 L alglucosidase alfa bioreactor crash occurred in September, 2009, at their Geel, Belgium facility, and another 2000 L bioreactor crash (during production of Cerezyme, an enzyme replacement therapy for Gaucher disease) occurred in May 2009 at the Allston Landing facility. Subsequently, the Applicant reported that the bioreactor crash was likely due to viral contamination with Vesivirus 2117. These bioreactor crashes have led to further drug shortage issues with the 2000 L product, as well as Cerezyme, and Fabrazyme, an enzyme replacement therapy for Fabry disease. All of these treatments are produced at the Allston Landing facility with the 2000 L bioreactor process. An analysis of these bioreactor crashes has thus far failed to determine a root cause; however, the Applicant has stated that a contamination of raw materials used in the manufacturing process may be involved.

First Complete Response Submission

The New England District Office (NEDO) re-inspected the Allston Landing facility in May 2009, in follow-up for the deficiencies noted in the Warning Letter. However, this re-inspection was incomplete because the Applicant had not instituted full corrective actions at the facility by the time of the re-inspection. Therefore, a second re-inspection was required and occurred in late October 2009. Furthermore, in October 2009, the Agency was notified by the Applicant of a new manufacturing issue at the Allston Landing, MA facility involving the contamination of intravenous drug products, including 2000 L alglucosidase alfa, with visible foreign particulate matter (stainless steel, rubber stopper particles, human hair, cellulosic fibers, and blue fibers). The NEDO inspectors determined that the facility did not comply with requirements set forth in the 21 CFR 601.20 (a) and (d). As a result of the adverse findings, the New England District Office updated the firm's GMP profile to "further action indicated."

Thus, based on the adverse findings noted, the Applicant's CGMP profile continued to be classified as Official Action Indicated (OAI), an unacceptable compliance status. Therefore, the Office of Compliance issued memo recommending a withhold approval action be taken for the 2000 L product on November 6, 2009.

Current Submission

The reader is referred to the Division of Manufacturing Product Quality review by K. Suvarna, dated April 8, 2009 and team leader review by P. Hughes, dated April 12, 2010 for complete details.

As stated above, the Agency informed the Applicant during a teleconference on November 20, 2009 that manufacturing information and product quality information already submitted by the Applicant for the 4000 L bioreactor scale product under IND 10,780 could be submitted to address the deficiencies cited in the second Complete Response Letter. Therefore, the

Applicant withdrew the request for licensure of the Allston Landing facility where 2000 L product is manufactured, and requested licensure of the Genzyme Flanders and Waterford facilities for manufacture of the 4000 L product in the current submission. The Waterford, Ireland facility was inspected from October 21-30, 2009, and the Genzyme Flanders facility was inspected from September 21-29, 2009. The DMPQ reviews state that both manufacturing facilities are currently in compliance with CGMP requirements. Thus, there are no pending compliance actions at either manufacturing site that would prevent the approval of this BLA. Alternate testing sites for the drug substance and drug product include Genzyme Corporation in Framingham, MA and Allston, MA. Both of these laboratories have an acceptable compliance status.

Final Recommendation

The recommendation from the Office of Compliance, Division of Manufacturing and Product Quality is for approval of Lumizyme produced at the 4000 L bioreactor scale. Additionally, DMPQ recommends one post-marketing commitment study to qualify the (b) (4) cycle (see section 8.D. Post-marketing Requirements and Commitments).

4. Nonclinical Pharmacology/Toxicology

Initial Submission

The reader is referred to the Pharmacology/Toxicology Review by N. Mehta dated January 30, 2009 for complete information.

Two nonclinical pharmacology/toxicology studies were reviewed during the original review cycle, as well as cross-referenced nonclinical pharmacology/toxicology studies submitted under BLA 125141 for Myozyme. The Reviewer noted that the 2000 L product produced similar glycogen clearance as compared with Myozyme but the glycogen clearance assays used in these studies were insufficiently sensitive to establish comparability between the two products. Two other studies suggest that glycogen clearing activity appeared to be directly correlated with mannose-6-phosphate receptor binding affinity. Toxicology studies demonstrated no treatment-related effects on developmental parameters. Based on the results of a 6-month repeat-dose toxicity study of rhGAA in juvenile mice, the NOAEL of rhGAA was 20 mg/kg/every other week. The kidney and the thymus were the primary target organs of toxicity. Five reproductive toxicity studies showed no treatment-related effects on fertility or early embryonic development in mice, or on fetal development in rabbits. A special toxicology study demonstrated that methotrexate induced a long-lived reduction in alglucosidase alfa directed antibody responses.

The Reviewer recommended approval provided agreement could be reached regarding recommended labeling changes. No post-marketing commitments or requirements were recommended.

First Complete Response Submission

There were no nonclinical issues cited in the Complete Response letter. Thus, there were no nonclinical issues reviewed in this submission.

Current Submission

The Applicant submitted nonclinical pharmacology data supporting the comparability of the 4000 L and 2000 L scale products. However, the data submitted have all previously been reviewed by the Agency in the original review cycle. Therefore, there was no review of the data submitted in the current submission.

5. Clinical Pharmacology/Biopharmaceutics

Initial Submission

The reader is referred to the Clinical Pharmacology Reviews by J. I. Lee and the Pharmacometrics Review by J. Earp, both dated January 7, 2009, for complete information.

General clinical pharmacology and intrinsic factors potentially affecting elimination

The 2000 L product is a therapeutic protein product that is disintegrated to amino acid and it is not expected to be excreted.

Multiple-dose pharmacokinetic (PK) parameters of the 2000 L product were estimated in 32 patients with late-onset Pompe disease patients in LOTS. PK parameters (C_{max}, AUC_{inf}, clearance, V_{ss}, and effective half life) appear to be comparable at Weeks 0, 12, and 52.

Drug-drug interactions

No studies were conducted to evaluate drug-drug interactions.

Through QT (TQT) Study or other QT assessment

The 2000 L product is a biologic product. No TQT study or other QT assessment was performed.

Demographic interactions/special populations

No studies were done to evaluate the effects of demographic or special populations on the PK of the 2000 L product.

Immunogenicity

All patients in the 2000 L product-treated group tested positive for anti-rhGAA IgG antibodies as assessed by enzyme-linked immunosorption assay (ELISA) and confirmed by radio-immunoprecipitation assay (RIP). The median time to seroconversion was 4 weeks after exposure. Approximately 61% of the patients trended toward decreasing titers from peak to last observation with continued treatment. However, 9 of 59 (15%) of patients who developed positive IgG titers during the study had a persistently elevated IgG titer at the end of the study. The median peak titer was 6,400 (range 200 to 819,000), and the median last titer was 1,600.

None of the 60 IgG positive patients tested positive for inhibition of enzyme activity. However, 10 patients (17%) tested positive, 8 (14%) borderline positive, and 41 (68%) negative for inhibition of cellular uptake into fibroblast cells. Both high anti-rhGAA IgG antibody titers and positive inhibitory antibody status appeared to affect PK: five patients with the highest binding IgG titer also tested positive for inhibitory antibody, and these 5 patients had higher mean CL, lower C_{max}, and lower AUC than the 29 patients with negative status.

There is insufficient data, however, to indicate whether inhibitory or high IgG antibodies are responsible for the increased clearance.

The Pharmacometrics Reviewer noted that although the data suggested a trend towards higher improvement in the 6 minute walk test (6MWT) with higher IgG titers and possibly also with positive inhibitory antibody status, he felt that the clinical significance of high antibody titers or positive uptake inhibition status remains unclear. No change in % predicted FVC was noted. There was no apparent association between higher anti-rhGAA IgG titers and occurrence of infusion reactions.

The Clinical Pharmacology review team recommended an approval action, provided agreement could be reached regarding the recommended labeling changes. The review team also recommended that additional PK data be collected in Pompe patients less than 21 years of age to further characterize the PK profile in pediatric patients as part of a verification study. This recommendation has been incorporated into a post-marketing commitment (see section 8.D. Postmarketing Requirements and Commitments).

First Complete Response Submission

There were no clinical pharmacology issues cited in the Complete Response letter. Thus, there are no clinical pharmacology issues reviewed in the Applicant's current submission.

Current Submission

The 4000 L product demonstrated sufficient physicochemical comparability with the 2000 L product based on critical product quality attributes (see section 3.A). Additionally, the change in manufacturing process between the 2000 L and 4000 L production scales was not considered a major manufacturing process change. Therefore, additional clinical pharmacology data evaluating the comparability of the 4000 L and 2000 L production scales was not required for approval. Thus, there were no clinical pharmacology issues reviewed in the Applicant's current submission. One clinical pharmacology post-marketing commitment (PMC) study was reviewed during this review cycle

(b) (4)

This PMC was negotiated during the original review cycle to evaluate the 2000 L product and was modified during this review cycle to clarify that the 4000 L product will be studied under this PMC (see section 8.D. Post-marketing Requirements and Commitments).

6. Clinical Microbiology

There were no clinical microbiology issues presented in the original review. Thus, there are no clinical microbiology issues reviewed in the Applicant's current submission.

7. Clinical/Statistical- Efficacy

Initial Submission

The reader is referred to the CDTL Review by J. Ku dated February, 26, 2009, the

Clinical Review by L. Yao dated February 26, 2009, and the statistical review by L. Kammerman, dated February 9, 2009, for complete information.

The 2000 L product was studied in a multicenter randomized, double-blind, placebo-controlled trial of 90 late-onset Pompe disease patients (Late-Onset Treatment Study or LOTS). Enrollment was restricted to patients 8 years and older who were naïve to enzyme replacement therapy, ambulatory, did not require invasive ventilatory support, and had an FVC between 30 and 79% of the predicted normal value in a healthy population. Patients were randomized 2:1 to either 20 mg/kg administered intravenously every two weeks or placebo.

The original design of LOTS was a 52 week trial with the co-primary endpoints of 1) distance (meters) walked during the 6MWT at 52 weeks, adjusted for the baseline, and 2) upright % of predicted FVC at 52 weeks, adjusted for the baseline. The 6MWT was to be examined first; if the treatment effect was statistically significant, then the effect on % of predicted FVC would be evaluated. A computerized minimization algorithm, rather than blocked randomization, was used to randomize the patients. While the study was ongoing, the design was revised to an adaptive strategy in order to determine, through an interim analysis, the optimal duration of the study, and compare the two treatments over the course of the study rather than focusing on comparisons at 52 weeks. Adoption of this strategy resulted in an extension of the trial to 78 weeks, changes in the definition of the primary endpoints, and a decision to use a linear effects model that assumed the 6MWT and FVC results would change linearly over time.

When the trial was completed and data were unblinded, it was observed that patients experienced improvement in the 6MWT from baseline to week 26 and then plateaued rather than continuously improved throughout the 78 weeks. Thus, the results had not satisfied the model assumption of linearity. Additionally, assumptions about the variance were also violated. To mitigate the violation of these assumptions, the applicant presented statistical models that were not pre-specified. Further complicating the analysis of the results was the use of a minimization algorithm to maintain a 2:1 ratio (Lumizyme: placebo) within study sites and within strata defined by baseline values for the 6MWT and FVC. Re-randomization tests are the appropriate approach for assessing statistical significance when a minimization algorithm is used. Usually, the result from using re-randomizations tests is similar to the result from using classical tests. This was not the case in LOTS. For example, for the ANCOVA of the 6MWT, the p-value changed from 0.035 to 0.06 with re-randomization. Based on these complications, the statistical Reviewer concluded that the most appropriate analytic method to use to analyze the results from LOTS was an analysis of covariance model (ANCOVA).

Thus, the results from LOTS as analyzed using ANCOVA demonstrate that after 78 weeks, the mean 6MWT increased by 25 meters for the 2000 L product-treated patients and decreased by 3 meters for placebo-treated patients, indicating a treatment difference of 28 meters ($p=0.06$) (see Table 1). Additionally, the mean % predicted FVC at 78 weeks increased by 1.2% for the 2000 L product-treated patients and decreased by 2.2% for placebo-treated patients indicating a treatment difference of 3.4% (95% CI: 1.0, 5.8%, $p=0.004$) (see Table 2).

Table 1: Change from baseline in distance walked in 6MWT in meters

	2000 L N=60	Placebo N=30	Difference
<i>Summary statistics:</i>			
Mean (\pm SD) distance walked at baseline	332.2 (128.0)	314.06 (131.4)	n/a
Mean (\pm SD) change from baseline to last observation in distance walked	26.13 (51.3)	0.43 (37.76)	25.70
Median change from baseline to last observation in distance walked	16	0	16
<i>Results of ANCOVA*:</i>			
Mean (SE) change from baseline to last observation in distance walked, adjusted for baseline 6MWT stratification, FVC stratification, their interaction and baseline 6MWT	25.13 (7.57) 95% CI: (10.1, 40.1)	-2.99 (10.64) 95% CI: (-24.1, 18.1)	28.12 (13.10) 95% CI: (2.1, 54.1)

Table 2: Change from baseline in upright FVC (% predicted)

	2000 L N=60	Placebo N=30	Difference
<i>Summary statistics:</i>			
Mean (\pm SD) FVC at baseline	55.58 (14.5)	53.36 (15.4)	n/a
Mean (\pm SD) change from baseline to last observation in FVC	1.37 (5.0)	-1.82 (4.4)	3.19
<i>Results of ANCOVA*:</i>			
Mean (\pm SE) change from baseline to last observation in FVC, adjusted for baseline 6MWT stratification, FVC stratification, their interaction and baseline FVC	1.20 (0.68) 95% CI: (-0.16, 2.57)	-2.20 (.97) 95% CI: (-4.12, -0.28)	3.40 (1.19) 95% CI: (1.03, 5.77)

An Endocrinology and Metabolic Drugs Advisory Committee (EMDAC) was convened to obtain advice regarding the statistical and clinical review issues. The Advisory Committee voted 16-1 that the effectiveness of the 2000 L product had been demonstrated in LOTS, however, twelve members recommended that accelerated approval be granted based on the FVC findings. Under Accelerated Approval regulations, the Applicant would be required to perform a post-marketing verification study to confirm the clinical effectiveness of the 2000 L product. Additionally, the committee voted 17 to 0 to require post-marketing safety studies to address the concerns of anaphylaxis, immunogenicity, and potential chronic immune-mediated reactions. The committee members also recommended that a REMS be required to ensure the safe use of the 2000 L product.

First Complete Response Submission

The reader is referred to the Clinical Review by C. Mueller, dated November 10, 2009, for complete information.

As stated above, the Agency and Applicant agreed that additional information from the Pompe Registry, a multinational disease registry with clinical information collected in Pompe patients treated with the 2000 L product since 2006 may provide sufficient clinical outcome information to support regular approval for the 2000 L product. Therefore, additional clinical data from the Pompe Registry submitted as part of the Applicant's Complete Response might eliminate the requirement for approval under Subpart E, and the requirement to perform a verification study as stated in the Complete Response Letter issued on February 27, 2009. Thus, additional data submitted by the Applicant in their Complete Response includes clinical outcomes data from the Pompe Registry.

The Pompe Registry is a disease registry that was established as a post-marketing commitment as a condition for approval of Myozyme in 2006. The Registry was designed as a multi-center, multi-national, observational program, and was initiated in September, 2006. The primary objectives of this voluntary registry were to evaluate the long-term effectiveness and safety of available treatment options, including ERT, in patients with Pompe disease, and to enhance the understanding of the natural history of Pompe disease. The data collected are based on standard of care clinical assessments as determined by the patient's physician, but include recommended assessments such as demographic information, clinical examination and laboratory assessments, cognitive, motor, and developmental assessments, quality of life assessments, antibody testing for patients receiving ERT, and neuron-imaging studies. Long-term clinical outcomes such as survival, ventilator-free survival are also collected. It should be noted that the registry includes both prospectively and retrospectively collected data.

The Applicant submitted clinical data from the Pompe registry comparing clinical outcome in a subset of infantile-onset Pompe patients treated exclusively with the 2000 L product with an age and disease-matched historical control. The clinical outcome of primary interest was survival, but ventilator-free survival was also included. Use of an age and disease-matched cohort of infantile-onset patients would be expected to provide more definitive outcomes over an 18 to 24 month period as compared with late-onset patients, whose clinical course would not be expected to decline as rapidly. Additionally, the Applicant was aware of a cohort of infantile-onset patients treated exclusively with the 2000 L product because it has been approved for use in all Pompe patients outside the U.S. since 2006. Thus, evaluation of clinical outcomes in a cohort of infantile-onset Pompe patients from the Pompe registry was performed to establish supportive clinical efficacy of the 2000 L product.

Overall, there were 48 patients enrolled in the Pompe registry meeting these inclusion criteria. However, only 25 of these patients had not been previously studied or reported by the Applicant, or had received the 2000 L product or Myozyme exclusively. Of these 25 patients, 10 U.S. patients received Myozyme exclusively, and 15 ex-U.S. patients received the 2000 L product exclusively. The median duration of treatment, median age at first infusion, and median age at death or last follow-up were similar between the Myozyme and the 2000 L product treatment groups.

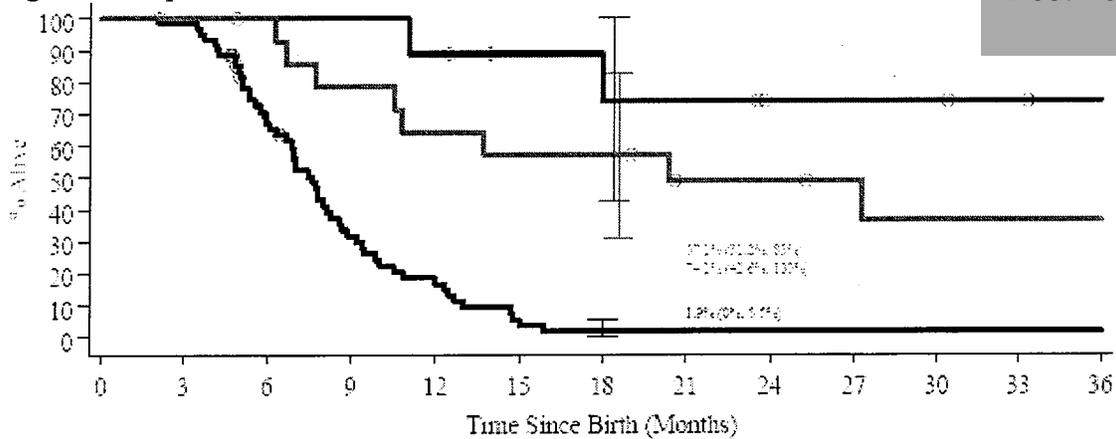
Based on data from natural history studies in infantile-onset Pompe disease, only 3% of patients survive past the age of 18 months. Therefore, the Applicant evaluated survival and ventilator-free survival at 18 months in the 2000 L product and Myozyme treated patients compared to this historical control population. There appears to be an increase in survival at 18 months in both the 2000 L product and Myozyme treatment groups compared with the historical control. Table 3 shows the overall survival by treatment group. The reviewer also notes an increase in survival in the Myozyme treatment group compared with the 2000 L product group, however, this analysis included only a small numbers of patients and, therefore, clear conclusions based on these observations cannot be made.

Table 3: Overall Survival

Survival	2000 L (%)	Myozyme (%)	Historical control (%)
Alive	5 (33)	8 (80)	1 (2)
Deceased	10 (67)	2 (20)	60 (98)
Total	15	10	61

As stated above, evaluation of survival at 18 months was of interest as this was the clinical endpoint used in AGLU1602. The Kaplan Meier estimate demonstrates a difference in survival at 18 months between patients treated with Myozyme or the 2000 L product and the historical control group (see Figure 1). Again, it is difficult to draw clear conclusions from these data based on the limited sample size, however, it should be noted that the 95% confidence intervals for the treated groups do not overlap with the historical control group, suggesting a substantive difference in survival. Table 3 shows *overall survival*, not survival at 18 months, and the reviewer also noted that (data not shown in the table 3) only 1/15 the 2000 L product-treated patients and 3/10 Myozyme patients were alive, but had not reached 18 months of age.

Figure 1: Kaplan-Meier estimate of time to death from date of birth



No. of Patients at Risk:

15	10	12	11	6	3	3	2	0	2	1	1	3
11	8	8	6	6	5	5	5	0	2	1	1	1
5*	6*	3*	1*	0	0	1	1	1	1	1	1	1

Electronically copied from Applicant's submission, page 77/82

The effect of Immunogenicity and cross-reacting immunologic material (CRIM) status was also evaluated in the registry population. However, of the 25 patients from the Pompe registry evaluated, only 17 patients had antibody information reported. Thus, it is not possible to evaluate the effect of immunogenicity on either safety or efficacy in these patients since this information was collected in a minority of patients evaluated. CRIM status for the 25 patients from the Pompe Registry included in the Complete Response was reviewed. CRIM status was available in 16/25 patients. Overall survival in CRIM negative patients was 20% (1/5 patients) in the 2000 L product group, whereas 100% of CRIM negative patients in the Myozyme group were alive. Additionally, 4/10 (40%) of the patients who died in the 2000 L product-group were CRIM negative, whereas none of the patients who died in the Myozyme group were CRIM negative. The data suggest that differences in CRIM status may contribute to the increase in mortality in the 2000 L product group, however, the numbers of patients is too small to establish clear conclusions regarding these data.

The clinical information provided by the Applicant provides additional clinical outcome information to support full approval for the 2000 L product. Specifically, the Applicant provides information from 25 infantile-onset patients from the Pompe Registry to support the overall clinical efficacy of the 2000 L product. The overall survival and survival at 18 months in the 2000 L product-treated patients compares favorably with an age-matched, diseased-matched historical control group. Eighteen month survival for the 2000 L product-treated patients was 57% compared with 1.9% in the historical control group. However, there were several concerns regarding the reliance of the Pompe Registry data in support of the clinical effectiveness of the 2000 L product. The Pompe Registry includes both prospectively and retrospectively obtained data and thus, inclusion of some patients retrospectively may be biased toward patients who had improved survival. Additionally, the overall numbers of patients are small, and there were no prospectively designed endpoints or statistical analysis plans. Therefore, despite the use of a cohort of infantile-onset patients treated with the 2000 L

product outside the U.S., the limitations of the Pompe Registry data prevented a recommendation for approval of the 2000 L product in the U.S. for all ages.

Current Submission

The information provided to support of the efficacy of the 4000 L product in the current submission relies on the physicochemical comparability between the 2000 L product and the 4000 L product. Therefore, no additional clinical studies were submitted in support of the clinical effectiveness of the 4000 L product.

Final Recommendation

The totality of clinical efficacy information submitted from the original BLA submission (LOTS) and the first complete response submission (Pompe registry) provide sufficient evidence of the effectiveness of Lumizyme in the treatment of late-onset Pompe disease. However, as stated in previous clinical reviews, the quantity and quality of data from the Pompe Registry are limited. Therefore, this Reviewer continues to recommend that Lumizyme should be limited to late-onset Pompe patients 8 years of age and older who do not have cardiac hypertrophy. Myozyme, approved for all Pompe patients, should be exclusively reserved for infantile-onset patients and late-onset patients less than 8 years of age for whom the efficacy and safety of Lumizyme has not been established.

Additionally, as stated above, the physicochemical comparability between the 2000 L and 4000 L products was established by the product quality review. Therefore, additional clinical data are not required to establish the effectiveness of the 4000 L product in late-onset Pompe disease. However, the Reviewer also notes that Myozyme and Lumizyme (2000 L product) were previously determined to be different products, not to be used interchangeably, based on important physicochemical differences that may lead to differences in potency. Thus, the 4000 L product must also be considered a different product from Myozyme, and cannot be used interchangeably based on physicochemical differences that may lead to differences in potency. This Reviewer recommends that a risk evaluation and mitigation strategy (REMS) be required (see section 13.C) to mitigate the potential 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 for whom the safety and effectiveness of Lumizyme have not been evaluated.

8. Safety

A. Clinical Site Inspections

Initial Submission

The Division of Scientific Investigations (DSI) performed clinical site inspections at 3 sites participating in LOTS and LOTS extension studies (Site #26 Erasmus Medical Center, the Netherlands; Site #4 Sophia's Children Hospital, the Netherlands; Site #29 Tower Hematology Oncology Medical Group, U.S.). The DSI inspector found that the data from the three sites inspected are reliable and can be used in support of the BLA (see section XI.A. for further details).

First Complete Response Submission

There were no issues cited in the Complete Response letter by the Division of Scientific Investigations. Thus, there were no clinical site inspections performed for this submission.

Current Submission

There were no issues cited in the Complete Response letter by the Division of Scientific Investigations. Thus, there were no clinical site inspections performed for this submission.

B. Safety

Initial Submission

The reader is referred to the CDTL Review by Joanna Ku dated February, 26, 2009, and the clinical review by L. Yao dated February 26, 2009, for complete information.

The primary safety information included data from LOTS, the only placebo-controlled study of the 2000 L product. Additional safety data as supportive evidence included interim safety data from the LOTS Extension Study (n=80) through April 15, 2008; data from 3 small open label studies of late (non-infantile) onset patients; data from the Myozyme Temporary Access Program (MTAP) (n=135); and data from world-wide post marketing safety reporting through April 15, 2008.

One death occurred, reported in a 33 year old woman who died of brain stem ischemia secondary to basilar artery thrombosis, a known complication of Pompe disease. The Reviewer concurred with the Applicant's assessment that the death was unrelated to the study drug.

Nine patients dropped out of the study (n=4 in the placebo group, and n=5 in the 2000 L product-treated group). In the placebo group, one patient was discontinued due to persistent headache, and three patients dropped out "wishing to receive commercial product." In the 2000 L product group, one patient died from brain stem ischemia; two patients were discontinued due to infusion reactions that were serious adverse events (anaphylaxis); one dropped out for personal reasons; and, one dropped out to receive commercial product. In the two patients who withdrew due to anaphylaxis as infusion reactions, one patient had anaphylaxis with laboratory confirmation of IgE mediated anaphylaxis, and the other developed severe angioneurotic edema after the third dose of 2000 L product, and based on the risk/benefit profile, the Investigator withdrew the patient from the study.

There was a total of 27 serious adverse events (SAEs), occurring in 19 patients. The SAEs that occurred at a higher incidence in the 2000 L product group than placebo included anaphylaxis, brain stem ischemia, coronary artery disease, angioneurotic edema, throat tightness, intervertebral disc protrusion, cerebral aneurysm, supraventricular tachycardia, gastroenteritis, chest pain/discomfort, pneumonia, and dehydration.

Anaphylaxis, allergic adverse reactions, and infusion reactions are the major safety concerns for the 2000 L product. Four cases of anaphylaxis were identified in LOTS, for an overall incidence anaphylaxis of the 2000 L product-treated patients of 4/60, or 6.7 %, compared with no cases in the placebo group. Anaphylaxis and severe allergic reactions have been observed in patients during and up to 3 hours after infusion of the 2000 L product.

Infusions reactions were also noted to be the most common adverse reaction with the 2000 L product. Notable infusion reactions that occurred in an incidence of at least 5% greater in the 2000 L product treatment group compared with placebo include anaphylaxis, urticaria, diarrhea, vomiting, dyspnea, rash, hematuria, and chest discomfort. Additionally, delayed infusion reactions, occurring up to 48 hours after the infusion include urticaria, dizziness, musculoskeletal weakness and pain. As some reactions occurred up to 48 hours after the infusion, they highlight the need for longer monitoring for delayed onset reactions. Additionally, the initial review also uncovered potential immune-mediated adverse reactions involving skin and kidney. There has been at least one report in the literature of the development of membranous glomerulonephritis associated with Myozyme treatment.

A review of the data submitted for review during the first cycle also includes interim data from the LOTS extension study, MTAP, and the Applicant's post-marketing pharmacovigilance database. There were no substantive differences in the types of adverse reactions noted in the primary review.

First Complete Response Submission

The reader is referred to the Clinical Review by C. Mueller for full details of the safety analysis.

The most relevant safety data included in this submission were from AGLU03206, LOTS extension. This study was conducted as an open-label, extension study for AGLU02704, LOTS, a double-blind, randomized, placebo-controlled study in 90 late-onset Pompe patients. In LOTS extension, 30 patients previously randomized to receive placebo, were started on treatment with the 2000 L product. Comparisons between these patients and patients treated with the 2000 L product in LOTS can be made. Safety data from the other sources (i.e., MTAP and spontaneous post-marketing reports) were also submitted, but these data are uncontrolled, and therefore, these data cannot be used to determine incidence rates for adverse events. However, these data were included to evaluate for any potential new safety signals from longer-term use of the 2000 L product.

Overall, the Applicant estimates that approximately 823 patients have received the 2000 L product exclusively in clinical trials and the postmarketing setting. LOTS extension includes 81 patients; all patients that completed LOTS also completed LOTS extension. Fifty-five patients were randomized in LOTS to receive the 2000 L product and continued to receive the 2000 L product in LOTS extension, and 26 patients were randomized in LOTS to receive placebo and received the 2000 L product in LOTS extension. There were 176 late-onset patients enrolled in MTAP, including 52 patients who were previously enrolled in either LOTS or LOTS extension. The remainder of patients reported in this submission (618) includes patients who the Applicant reports as having received only the 2000 L product, and no other production scales of alglucosidase alfa.

A total of 24 deaths were reported in the Complete Response as of the March 16, 2009 cutoff. The majority of deaths (21) were reported from the postmarketing setting. Of these 21 patient

deaths, 14 patients were infantile-onset patients, 5 were late-onset patients, and 2 were of unknown phenotype. The cause of death in these cases was cardiac or respiratory failure in the majority of cases. There were no deaths reported during LOTS extension.

There were a total of 27 serious adverse events (SAEs) previously reported in 19 patients in LOTS. An additional 5 SAEs in 3 new patients (16705, 65713, and 18702), were reported in the LOTS extension safety data submitted in the Complete Response. The SAEs reported in these new patients included cervical carcinoma stage II, nephrolithiasis, renal cyst, and gastric ulcer. These SAEs were all assessed as not related to treatment with the 2000 L product, and this Reviewer agrees with the Applicant's assessment of relationship to treatment. There were an additional 28 SAEs reported in 8 patients from MTAP, and 54 SAEs in 17 late-onset patients reported in the post-marketing setting. The majority of SAEs reported in the post-marketing setting were characterized by the Applicant as infusion reactions and include urticaria, facial edema, fever, irritability, decreased oxygen saturation, and tachypnea. Anaphylaxis, pneumonia, respiratory and cardiac failure were also noted.

Anaphylaxis, allergic adverse reactions, and infusion reactions remain the major safety concerns with the 2000 L product. Based on a review of the adverse events from LOTS extension, two additional patients (29705 and 18708) appear to have developed anaphylaxis during LOTS extension. The Applicant has also reported 3 patients (50018, 50091, and 10523) in MTAP with signs and symptoms consistent with anaphylaxis during the safety update period.

Infusion reactions (50% of patients in LOTS) remain the most common adverse event with the 2000 L product. Noteworthy infusion reactions that were reported in at least one patient include angioneurotic edema, hypertension, lip or tongue swelling, wheezing, oral pruritis, tachycardia, and photophobia. Other common adverse events, seen in at least 20% of patients, included falls, musculoskeletal pain/myalgia/muscle spasms, nasopharyngitis, headache, dizziness, diarrhea, arthralgia, hypoacusis, nausea, vomiting, fatigue, back pain, peripheral edema, and fever. The types of common adverse events and infusion reactions appears to be consistent between the LOTS and combined LOTS and LOTS extension data, suggesting that these adverse events are more likely during or immediately after infusion with the 2000 L product.

Other significant adverse events that were uncovered during the original BLA review include the possibility of chronic, immune-mediated skin and kidney adverse reactions. The clinical reviewer notes that additional potential immune-mediated skin and kidney adverse reactions appear in both LOTS extension data, and MTAP. Long-term follow up for potential chronic immune-mediated adverse events was agreed upon with the Applicant as a post-marketing requirement.

Current Submission

The reader is referred to the Clinical Review by C. Mueller for full details of the safety analysis.

The safety data included in this submission were from AGLU03907, the Alglucosidase alfa Temporary Access Program, an expanded access program designed to provide treatment to adult Pompe patients in the U.S. pending approval of the 4000 L product. Additional safety data were also obtained from the ex-U.S. postmarketing experience with the 4000 L product. Both of these sources of data are uncontrolled, and therefore, were not reviewed to determine incidence rates for adverse events. However, these data were included to evaluate for any potential new safety signals for the 4000 L product.

The safety data from AGLU03907 were extremely limited. Only 128 patients received at least one infusion with 4000 L product and the maximum exposure to 4000 L product from this study was three doses over a period from October 19, 2009 to November 24, 2009 (approximately 6 weeks). In contrast, the exposure to the 2000 L product in this study ranged from 2 to 133 doses over 4 to 267 weeks. Additionally, the majority of patients had previously received 2000 L product prior to receiving 4000 L product. Therefore, clear differences between the safety profile of the 2000 L product and the 4000 L product could not be established from the data provided.

There were no deaths in AGLU03907 during the 6-week period studied. One serious adverse event was reported; a 55 year-old female with late-onset Pompe disease who was hospitalized for vomiting and diarrhea and was diagnosed with viral gastroenteritis. This adverse event was determined by the Applicant to be unrelated to treatment with 4000 L product. There were no patient dropouts or discontinuations during the period studied.

There were no reports of anaphylaxis, skin, kidney or other potentially immune-mediated adverse events during the period studied. One patient experienced an infusion reaction. However, as mentioned previously, the data provided covered only a 6-week period and the maximum exposure was 3 doses during this period. Therefore, there are inadequate data to evaluate clearly establish clinical safety profile of the 4000 L product compared to the 2000 L product.

The postmarketing safety data for the 4000 L product provided by the Applicant included data from December 29, 2008 to September 28, 2009 and additional reports through November 24, 2009. The 4000 L product has been available outside the U.S. since March 3, 2009. The Applicant estimated that approximately (b) (4) patients received at least one dose of 4000 L product during this period, but due to the nature of post-marketing safety information collected, the Applicant is not able to clearly establish the specific scale product the patient was receiving in all cases. Again, due to the quality of these data, clear differences between the safety profile of the 2000 L product and the 4000 L product could not be established from the data provided.

The Applicant reported 30 patient deaths (all ex U.S.) during the period evaluated. Seven deaths occurred during treatment with 4000 L product (4 patients with infantile-onset, and 3 patients with late-onset). The majority of deaths were assessed as related to the underlying Pompe disease and not related to treatment. A total of 70 serious adverse events were reported in patients receiving 4000 L product. The types of serious adverse events (anaphylaxis, infusion reactions, respiratory distress, pneumonia, septic shock, cough, and respiratory

disorder) did not differ substantially from serious adverse events previously noted in patients treated with 2000 L product. There were no reports of immune complex-mediated reactions involving the skin or kidneys. Again, the quantity and quality of the post-marketing data are insufficient to clearly establish a similar clinical safety profile of the 4000 L product compared to the 2000 L product.

Final Recommendation

The safety data on the 4000 L product included by the Applicant are insufficient to clearly establish a similar clinical safety profile of the 4000 L product compared to the 2000 L product. However, the product quality data appear to establish comparable if not improved critical product quality attributes between the 4000 L and 2000 L scale products. Therefore, the overall clinical safety information provided in this submission are sufficient when combined with information already reviewed in previous submissions for the 2000 L product. Anaphylaxis and infusion reactions continue to be important safety concerns, as well as the potential for chronic immune-mediated (e.g., skin and kidney) adverse reactions, based on safety findings for the 2000 L product. These safety findings warrant the placement of a boxed warning in the product labeling (see section 12, labeling), implementation of a Risk Evaluation and Mitigation (REMS) program (see section 13.C.) to ensure that the known risks of anaphylaxis and severe allergic reactions, and the potential risks of severe cutaneous and systemic immune-mediated reactions to Lumizyme are communicated to patients and prescribers, and the initiation of post-marketing requirement and commitment studies (see section 8.D.) to evaluate the long-term safety and effectiveness of Lumizyme in patients with late-onset Pompe disease.

9. Advisory Committee Meeting

Initial Submission

The reader is referred to the Clinical Review of the original BLA 125291 submission by L. Yao for details of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting held on October 21, 2008.

The EMDAC was convened to obtain advice regarding statistical and clinical review issues as described above. The committee voted 16 to 1 to approve the 2000 L product based on the clinical data presented. However, the majority of the committee recommended approval under Accelerated Approval (21 CFR 601 Subpart E), based on improvement in % predicted FVC. Under Accelerated Approval regulations, the Applicant would be required to perform a post-marketing verification study to confirm the clinical effectiveness of Lumizyme. The committee also voted 17 to 0 to require post-marketing safety studies to address the concerns of anaphylaxis, immunogenicity, and potential chronic immune-mediated reactions. The committee members also recommended that a REMS be required to ensure that the benefits of Lumizyme outweigh the risk.

First Complete Response Submission

There was no advisory committee meeting convened during this review cycle.

Current Submission

There was no advisory committee meeting convened during this review cycle.

10. Pediatrics

Alglucosidase alfa received orphan designation in August, 1997. Therefore, the regulations that pertain to the Pediatric Equity in Research Act (PREA) do not apply to Lumizyme. Additionally, there were no pediatric consults obtained either during the first review cycle, second review cycle, or the present review.

11. Other Relevant Regulatory Issues

A. DSI audits

Initial Submission

The Division of Scientific Investigations (DSI) performed clinical site inspections at 3 sites (Site #26 Erasmus Medical Center, the Netherlands; Site #4 Sophia's Children Hospital, the Netherlands; Site #29 Tower Hematology Oncology Medical Group, U.S.). The DSI inspector found that the data from the three sites inspected are reliable and can be used in support of the BLA.

Financial disclosures were submitted by the Applicant during the first review cycle and include two notable findings for the LOTS and LOTS extension studies: One site investigator (b) (6) received grants, equipment payments, consultation payments and retainers totaling over €1,139,000 from (b) (6), and an additional \$940,246.00 in royalties and payments upon FDA and EMEA approval of Myozyme between (b) (6). Another investigator for a U.S. transfer site (b) (6) received royalties and payments upon FDA approval of Myozyme of \$7,914,895 and an additional \$468,715 in grants, retainers, honoraria, and retainers from (b) (6). Despite the significant financial relationships between these two investigators and the Applicant, the conduct of the studies does not appear to have been affected by these financial arrangements.

First Complete Response Submission

There were no issues cited in the Complete Response letter by the Division of Scientific Investigations. Thus, there were no clinical site inspections performed for this submission.

Current Submission

There were no issues cited in the Complete Response letter by the Division of Scientific Investigations. Thus, there were no clinical site inspections performed for this submission.

B. Clinical Consults

There were no clinical consults obtained in the original review, first complete response submission, or for the current review.

C. Drug Shortage

Drug Shortage History

There has been a persistent drug shortage of Myozyme since the first quarter of 2007. The cause of this drug shortage is multifactorial, and includes issues such as manufacturing constraints with Myozyme, management decisions against increasing Myozyme production in favor of pursuing unapproved larger scale production (i.e., 2000 L and 4000 L products), comparability concerns between Lumizyme and Myozyme, contamination events (Vesivirus and visible particulate matter) at the Applicant's manufacturing facilities, and management decisions to cease production of the 2000 L product. Therefore, Myozyme has been reserved for infants and children up to 18 years of age. The 2000 L scale product was made available to only those adult Pompe patients who are wheelchair bound or required ventilatory assistance under an expanded access program known as the Myozyme Temporary Access Program (MTAP). Approximately 180 adult patients with Pompe disease who met inclusion criteria received 2000 L product through this expanded access program. However, the Applicant made a decision to close MTAP to new enrollment in April, 2008. Between April 2008 and October 2009, The Agency was aware of approximately 50 to 150 patients with late-onset (non-infantile) Pompe disease in the U.S. who had no access to alglucosidase alfa treatment because of the Applicant's decision to close the expanded access program to new enrollment.

In August, 2009, an amendment to MTAP was received by the Agency, to allow use of 4000 L alglucosidase alfa in patients currently enrolled in this treatment protocol and to change the name of the protocol to the Alglucosidase alfa Temporary Access Program (ATAP). This amendment was intended to conserve the supply of the 2000 L product for patients awaiting treatment after the anticipated U.S. approval of the 2000 L product in November 2009. However, this protocol amendment specifically did not allow for enrollment of new patients.

After discussions between Genzyme and the Commissioner of FDA in August and October, 2009, Genzyme agreed to re-open ATAP to all Pompe patients meeting enrollment criteria. These enrollment criteria include patients who are wheelchair-bound, or require ventilatory assistance. The Agency recommended that Applicant broaden the enrollment criteria for ATAP to include all patients for whom their treating physician determines medical need; however, the Applicant did not modify enrollment for ATAP. This Reviewer is also aware of at least 4 patients who are been granted treatment with 2000 L or 4000 L product under emergency IND use since ATAP was re-opened to enrollment. Approval of Lumizyme will likely eliminate the current U.S. drug shortage issue for patients with Pompe disease.

12. Labeling

A. Proprietary Name

Initial Review

During the initial review cycle, the originally proposed trade name of "Myozyme" was submitted for the 2000 L product. A review of the trade name was performed by Z. Oleszczuk in the Division of Medication Errors Prevention and Analysis (DMEPA). DMEPA expressed concern over a potential name confusion that could lead to medication errors given that the trade name "Myozyme" has been in use since 2006 for the 160 L product. The Applicant

withdrew the proposed trade name of “Myozyme” and proposed other trade names including “Lumizyme.” Lumizyme was found to be acceptable by DMEPA.

First Complete Response Submission

A re-review of the trade name was performed by Z. Oleszczuk in the Division of Medication Errors Prevention and Analysis (DMEPA). The tradename “Lumizyme” was found to be acceptable by DMEPA.

Current Submission

In the current review cycle, a re-review of the trade name was performed by Z. Oleszczuk in the Division of Medication Errors Prevention and Analysis (DMEPA). The tradename “Lumizyme” was found to be acceptable by DMEPA.

B. Physician Labeling / Carton and Container Labeling

Final labeling for Lumizyme was also satisfactorily negotiated during the current review cycle. The final labeling conforms to the Physician Labeling Rule (PLR) format. The reader is referred to final labeling for Lumizyme for complete details. Highlights of final labeling for Lumizyme are presented below.

1. Boxed Warning

A boxed warning was included in the labeling to inform prescribers about the risk of life-threatening anaphylactic and severe allergic and immune-mediated reactions during Lumizyme infusions. Additionally, the boxed warning also informs prescribers about the potential risk of rapid disease progression in Pompe patients less than 8 years of age, and the restricted distribution program called the Lumizyme ACE Program (see section XII.C.).

2. Indication

The indication for Lumizyme is restricted to patients 8 years of age and older with late (non-infantile) onset Pompe disease who do not have evidence of cardiac hypertrophy. The safety and efficacy of LUMIZYME 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.

3. Warnings and Precautions

The Warnings and Precautions section includes information regarding the most serious adverse reactions associated with Lumizyme and information regarding the restricted distribution program. These warnings include the risk of anaphylaxis, severe allergic and immune-mediated reactions, the risk of acute cardiopulmonary failure, and information regarding the Lumizyme ACE Program, precautions when administering general anesthesia to Pompe patients, and the need to monitor anti-rhGAA antibody levels while receiving Lumizyme.

4. Use in Specific Populations: Pediatric Use

The labeling informs prescribers that Lumizyme is not indicated for patients 8 years of age and younger due to lack of efficacy data in patients 8 years of age and younger and because of the risk of rapid disease progression in younger patients. However, the labeling does not

explicitly state that Myozyme is available for use in infantile-onset Pompe patients or in late-onset Pompe patients 8 years of age and younger.

5. Description

This section discusses the structure and biochemical properties of Lumizyme. The section also states that Myozyme and Lumizyme are produced using different manufacturing processes.

(b) (4)

6. Clinical studies

The clinical studies section includes data from both controlled studies (i.e., LOTS) and uncontrolled studies (i.e., the Pompe Registry) used to support the clinical effectiveness of Lumizyme. This section does not include information regarding potential differences in clinical effectiveness between Lumizyme and Myozyme.

7. Patient Counseling Information

This section includes information to prescribers regarding the Lumizyme ACE Program, the Pompe Registry, and the most common adverse reactions associated with Lumizyme (i.e., infusion reactions).

8. Medication Guide

A medication guide was not included in the REMS because patients treated with Lumizyme would be expected to receive treatment only at specialized infusion centers under the supervision of trained personnel.

Current Submission

There were only minor changes made to the labeling during the current review cycle. These changes include strengthening the language regarding the use of an in-line filter in the Dosage and Administration section; and additional nonclinical information added to Section 8.1 (Use in Specific Populations; Pregnancy Category B Section), and modifications regarding the Lumizyme ACE program in Warnings and Precautions (Section 5.3: Distribution Program for Lumizyme) and Patient Counseling Information (Section 17: Distribution Program for Lumizyme).

13. Recommendations/Risk Benefit Assessment

A. Recommended Regulatory Action

In the opinion of this reviewer, the data provided in this complete response support the approval of Lumizyme for treatment of patients 8 years of age and older with late (non-infantile) onset Pompe disease who do not have evidence of cardiac hypertrophy. The product quality data in this complete response submission provided sufficient information to establish the biochemical comparability between the 4000 L and 2000 L products based on critical product quality attributes. Therefore, the clinical data provided in this and previous complete response submissions provides sufficient evidence of the safety and effectiveness of Lumizyme for treatment of patients 8 years of age and older with late (non-infantile) onset Pompe disease who do not have evidence of cardiac hypertrophy. The data in this and two

previous complete response submissions also provide sufficient information to construct product labeling that is necessary for the safe and effective use of the product in patients with late-onset Pompe disease, 8 years of age and older. I am in agreement with the recommendation for the implementation of a REMS to ensure the benefits of treatment with Lumizyme outweigh the risks (see section 13.C). I am also in agreement with the recommendation for two clinical post-marketing requirement studies; and 15 post-marketing commitment studies (3 clinical, 11 CMC, and 1 clinical pharmacology) (see section 13.D). The clinical and clinical pharmacology PMC studies were negotiated as post-approval studies because of the current drug shortage and the current urgent need for available treatments for Pompe disease in the U.S. All of the clinical studies require long-term evaluation that cannot be completed in a timely manner, but will likely provide additional clinical efficacy and information when completed. The CMC PMC studies were also negotiated as post-approval studies because of the current drug shortage. These studies will promote improved product quality, but were not assessed as critical to the approval of Lumizyme. The clinical pharmacology CMC will provide pharmacokinetic information to support labeling of Lumizyme in pediatric patients age 8-18 years, for which there are only limited data available from LOTS.

B. Risk Benefit Assessment

I am in agreement with the overall recommendation for an Approval action from the product quality and clinical reviewers. The data presented in the second complete response support the comparability of the 4000 L scale product to the 2000 L scale product. The overall safety and effectiveness of the 2000 L product was demonstrated in data presented in the two previous review cycles. Thus, with the establishment of physicochemical comparability between the 4000 L and 2000 L scale products, the data support the overall safety and effectiveness of Lumizyme (4000 L scale product) in the treatment of patients 8 years of age and older with late (non-infantile) onset Pompe disease who do not have evidence of cardiac hypertrophy. However, the safe use of Lumizyme cannot be established without the implementation of a REMS. Additionally, the long-term safety and effectiveness of Lumizyme cannot be established without the recommended nonclinical, clinical pharmacology, and clinical postmarketing requirement and commitment studies (see Section 13.D).

C. Recommendation for Postmarketing Risk Evaluation and Management Strategies

Initial Submission

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Food Drug and Cosmetic Act (FDCA) to authorize 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)). This provision took effect on March 25, 2008.

A REMS was required by the Applicant to mitigate the potential 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 for whom the safety and effectiveness of Lumizyme have not been evaluated, and to ensure that the known risks of anaphylaxis and severe allergic

reactions, and the potential risks of severe cutaneous and systemic immune-mediated reactions to Lumizyme are communicated to patients and prescribers. However, a complete REMS was not agreed upon during the first cycle. The Applicant was required to submit a revised REMS with the Complete Response that included a communication plan, elements to assure safe use (ETASU), an implementation system, and a timetable for assessments.

First Complete Response Submission

The Applicant submitted a revised, proposed REMS with the Complete Response. During the current review cycle, a satisfactory REMS was negotiated with the Applicant. The Applicant's REMS program, entitled, "The Lumizyme Access, Control, and Education (ACE) Program" includes all components of a REMS to ensure that the benefits of Lumizyme outweigh the risk. A medication guide was not included in the REMS because patients treated with Lumizyme would be expected to receive treatment only at specialized infusion centers under the supervision of trained personnel. Therefore, the Lumizyme REMS includes the following elements:

1. Goals

- To mitigate the potential risk of rapid disease progression in infantile-onset Pompe patients and patients with late (non-infantile) onset disease less than 8 years of age for whom the safety and effectiveness of Lumizyme have not been evaluated
- To ensure that the known risks of anaphylaxis and severe allergic reactions associated with the use of Lumizyme are communicated to patients and prescribers, and to ensure that the potential risks of severe cutaneous and systemic immune mediated reactions to Lumizyme are communicated to patients and prescribers

2. Communication plan

- Communication plan will include introductory letters that will be provided to anyone who will receive, prescribe, administer, or dispense Lumizyme. The communication plan will also provide information regarding the Lumizyme ACE Program.

3. Elements To Assure Safe Use

- Requirement for patients, healthcare facilities, and prescribers to enroll in the program
- A training module for healthcare facilities and prescribers
- A restricted distribution system to ensure that only patients enrolled in the program receive Lumizyme, and that only prescribers and healthcare facilities enrolled in the program are able to prescribe and administer Lumizyme

4. Implementation System

- Requirement for Genzyme to maintain a validated and secure database of certified physicians, healthcare facilities, and patients enrolled in the Lumizyme ACE Program
- Requirement for Genzyme to monitor re-enrollment of certified participants
- Requirement for Genzyme to monitor healthcare facilities and providers to ensure only enrolled patients receive Lumizyme

5. System of Assessments

- Genzyme will submit REMS assessments to FDA 6 months and 1 year after the date of approval of the Lumizyme ACE Program, and then annually thereafter.

Current Submission

There were no substantive changes made to the REMS during the current review cycle. The REMS received final clearance by the Safety Review Team (SRT).

D. Recommendation for other Postmarketing Requirements and Commitments

Initial Submission

Title IX, Subtitle A, Section 901 of the FDAAA amends the FDCA to authorize 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)). This provision took effect on March 25, 2008.

Based on the review of the safety data provided by the Applicant, serious adverse reactions, including anaphylaxis and immunologically mediated reactions have been noted. In order to more fully characterize these safety findings, two clinical postmarketing requirements (PMRs) were agreed upon during the first review cycle and are listed below:

1. A retrospective immunogenicity study based on the pattern of antibody responses in patients enrolled in the LOTS and LOTS Extension Studies. The objective of this study is to determine which immunogenicity profiles may predict the development of the known serious risks of treatment with Lumizyme, including anaphylaxis, severe allergic reactions, and signals of severe cutaneous and systemic immune complex-mediated reactions.



2. A prospective safety study conducted within the ongoing Pompe Registry to assess the known serious risks of treatment with Lumizyme, including anaphylaxis, severe allergic reactions, and signals of severe cutaneous and systemic immune complex-mediated reactions. This sub-study will assess the occurrence of these adverse events

and the effect of antibody responses (both timing and pattern of responses) and CRIM status (only on infantile-onset patients) on the occurrence of these events.

Additionally, two clinical postmarketing commitments were agreed upon during the first review cycle, and were included in the resubmission.

First Complete Response Submission

Both clinical PMRs that were agreed upon during the first cycle review were included in the Complete Response and are listed below. However, the content of these PMRs was shortened during this review cycle to conform to the preferred PMR content. The reviewer notes that information that was removed from the original clinical PMRs should be incorporated into the final protocol for each PMR. Therefore, the original language used during the first cycle review is included above.

1. A retrospective immunogenicity study based on the pattern of antibody responses in patients enrolled in the Late Onset Treatment Study (LOTS) and LOTS Extension Studies. The objective of this study is to determine which immunogenicity profiles may predict the development of (b) (4) anaphylaxis and severe allergic reactions, and (b) (4) immune complex-mediated reactions with Lumizyme (alglucosidase alfa) treatment.
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.

Three clinical post-marketing commitment (PMC) studies that were agreed upon with the Applicant during the first review cycle were included in the Complete Response. Additionally, four CMC PMC studies and one clinical pharmacology PMC study were negotiated during the current review cycle. The clinical and clinical pharmacology PMC studies were negotiated as post-approval studies because of the current drug shortage and the current urgent need for available treatments for Pompe disease. All of the clinical studies require long-term evaluation that cannot be completed in a timely manner, but will likely provide additional clinical efficacy and information when completed. The clinical pharmacology CMC will provide pharmacokinetic information to support labeling of Lumizyme in pediatric patients age 8-18 years, for which there are only limited data available from LOTS. The CMC PMC studies were also negotiated as post-approval studies because of the current drug shortage. These studies will promote improved product quality, but were not assessed as critical to the approval of Lumizyme. The 8 PMC studies are listed below:

(b) (4)

(b) (4)

2. A long-term follow-up study of patients in LOTS and LOTS Extension Studies whose response to Lumizyme (alglucosidase alfa) is associated with substantial improvement over baseline in the 6MWT results. This study will be conducted as a sub-study within the ongoing Pompe Registry.
3. As part of 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). (b) (4)
4. Genzyme commits to evaluate the use of the (b) (4) method as a release test for glycan profiling of the drug substance.
5. Genzyme commits to develop an analytical method to monitor (b) (4) microns in size and evaluate its use in the release and stability specifications.
6. Genzyme commits to evaluate the use of the (b) (4) assays in the drug product stability program.
7. 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.
8. A prospective pharmacokinetic (PK) study will be conducted to characterize the pharmacokinetics of Lumizyme in pediatric patients ranging in age from 8 to 18 years of age. The study will be comprised of approximately 20 patients. Pharmacokinetic blood samples will be collected pre-dose and throughout the dosing interval or until Lumizyme concentrations are unquantifiable following first dose and at Weeks 12 and 26. The study will also analyze the effect of immunogenicity (anti-rhGAA IgG titers and inhibitory/neutralizing antibodies) on the pharmacokinetic profile of Lumizyme. Pharmacokinetic assessments will be conducted using a validated assay and will be calculated both with and without correcting for endogenous levels of rhGAA.

Current Submission

Both clinical PMR studies that were agreed upon during the first cycle (original) review were included in the current submission and are listed below. However, the content of

these PMR studies was further shortened during this review cycle to conform to the current PMR template. The reviewer notes that the language in the first PMR study was changed slightly during the current review cycle, but the intent of the PMR study has not changed.

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.
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.

Three clinical PMC studies, one clinical pharmacology PMC study, and 4 CMC PMC studies that were agreed upon with the Applicant during the first two review cycles were included in the Complete Response. During the current review cycle, several modifications and additions to the existing CMC PMC studies were negotiated. The clinical and clinical pharmacology PMC studies were negotiated as post-approval studies because of the current drug shortage and the current urgent need for available treatments for Pompe disease. All of the clinical studies require long-term evaluation that cannot be completed in a timely manner, but will likely provide additional clinical efficacy and information when completed. The clinical pharmacology CMC will provide pharmacokinetic information to support labeling of Lumizyme (4000 L product) in pediatric patients age 8-18 years, for which there are only limited data available from LOTS. The CMC PMC studies were negotiated to further characterize and validate the 4000 L production processes and were also negotiated as post-approval studies because of the current drug shortage. These studies will promote improved product quality, but were not assessed as critical to the approval of Lumizyme. The following 15 PMC studies (three clinical, eleven CMC, and one clinical pharmacology) are listed below:

1. 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.
2. A long-term follow-up study of patients in LOTS and LOTS Extension Studies whose response to Lumizyme (alglucosidase alfa) is associated with substantial improvement over baseline in the 6MWT results. This study will be conducted as a sub-study within the ongoing Pompe Registry.
3. 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). (b) (4)

4. To evaluate the use of the (b) (4) method as a release test for glycan profiling of the drug substance.
5. To develop an analytical method to monitor (b) (4) and evaluate risk to product quality and proposed risk mitigation strategies.
6. 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.
7. To develop and qualify an in-house 4000 L reference standard.
8. 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).
9. To add the (b) (4) test to the stability specifications for 4000 L drug substance.
10. To add the (b) (4) test to the release and stability specifications for 4000 L drug product.
11. To re-evaluate and optimize the (b) (4) hold time to improve (b) (4) species for the 4000 L product.
12. To re-evaluate and revise the acceptance criterion for Km measured by the (b) (4).
13. 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).
14. To qualify the (b) (4) for its intended use by performing an equivalency test between the D value of (b) (4) and (b) (4).
15. A prospective pharmacokinetic (PK) study conducted within the ongoing Pompe Registry study to characterize the pharmacokinetics of Lumizyme in pediatric patients in the age range of 8 years to 18 years.

E. Recommended Comments to Applicant

Based on the recommended Approval action for Lumizyme, the recommended comments to the Applicant include a provision for a REMS, and additional post-marketing requirement

(PMR) and commitment (PMC) studies. The REMS is discussed in section 13.C and specific PMR and PMC studies are discussed in section 13.D.

The reader is directed to the Approval Letter for specific details.