CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125291

SUMMARY REVIEW

Division Director Summary Review

Date	May 24, 2010
From	Donna Griebel, MD 5/24/2010
Subject	Division Director Summary Review
BLA	STN 125291
Applicant Name	Genzyme Corporation
Date of Submission	December 16, 2009
PDUFA Goal Date	June 17, 2010
Proprietary Name / Established (USAN) Name	Lumizyme alglucosidase alfa
Dosage Forms / Strength	Sterile lyophilized powder for reconstitution for intravenous administration/50 mg vial
Proposed Indication(s)	Treatment of patients 8 years and older with late (non-infantile) onset Pompe disease [α-glucosidase (GAA) deficiency] 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.
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Christine Mueller, D.O./Lynne Yao, MD
Biostatistical Review	Lisa Kammerman, PhD/Mike Welch, PhD
Pharmacology Toxicology Review	Ke Zhang, Ph.D./Niraj Mehta, Ph.D./ David Joseph, Ph.D.
Clinical Pharmacology Review	Jang-Ik Lee, Pharm.D., Ph.D/Sue-Chih Lee, Ph.D Justin Earp, Ph.D./Yaning Wang, Ph.D. Tien-Mien Chen, Ph.D.
Product Quality Review	Juhong Liu, Ph.D.
Microbiology Review	Kalavati Suvarna, Ph.D.
Product Quality Executive Review	Emanuela Lacana, Ph.D./B.Cherney, Ph.D./Amy Rosenberg, MD
CDTL Review	Lynne Yao, MD
OSE/DMEPA	Zachary Oleszczuk, Pharm.D.

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
CDTL=Cross-Discipline Team Leader

Division Director Summary Review

1. Introduction

In this application, Genzyme Corporation proposes to market Lumizyme (alglucosidase alfa) for treatment of patients 8 years and older with late (non-infantile) onset Pompe disease [acid α-glucosidase deficiency] who do not have evidence of cardiac hypertrophy. Alglucosidase alfa is the human enzyme acid α-glucosidase (GAA) produced by recombinant technology in a Chinese hamster ovary cell line. This BLA has been subject to more than one CR action and the product that will be marketed, the 4000 L bioreactor scale product[1], was not the original bioreactor scale product (2000 L)[2] submitted in the initial BLA submission.

The currently marketed alglucosidase alfa product, Myozyme, is produced at a 160 L bioreactor scale. Its indication is: "for treatment of patients with Pompe disease. Myozyme has been shown to improve ventilator-free survival in patients with infantile-onset Pompe disease as compared to an untreated historical control, whereas use of Myozyme in patients with other forms of Pompe disease has not been adequately studied to assure safety and efficacy." Although this indication does not limit Myozyme's use to treatment of patients with infantile onset Pompe disease, its production scale (160 L) has limited its availability for the overall Pompe disease population. Myozyme has been reserved for infants and children up to 18 years of age.

I concur with the recommendations of the reviewers that this BLA for Lumizyme 4000 L should receive an Approval action for the following indication: "treatment of patients 8 years and older with late (non-infantile) onset Pompe disease [acid α-glucosidase (GAA) deficiency] who do not have evidence of cardiac hypertrophy." I concur with the reviewers that the product can only be approved with a Risk Evaluation Mitigation Strategy (REMS), and I concur with its communication plan, component elements to ensure safe use, implementation system and timetable for submission of assessments. The goals of the REMS are: 1) 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 2) 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. In addition, I agree that the Applicant should be required to conduct postmarketing studies of Lumizyme to assess the known serious risks of anaphylaxis and severe allergic reactions, and signals of severe cutaneous and systemic immune complex-mediated reactions.

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[1] Lumizyme (alglucosidase alfa) produced at the 4000 L scale will be referred to as Lumizyme 4000 L.
[2] Lumizyme (alglucosidase alfa) produced at the 2000 L scale will be referred to as Lumizyme 2000 L

2. Background

Pompe disease is a rare, autosomal recessive disorder of glycogen metabolism caused by the absence or deficiency of acid-α-glucosidase (GAA), a lysosomal enzyme. Accumulation of lysosomal glycogen impacts the liver and cardiac and skeletal muscle. Patients develop severe and progressive muscle weakness, cardiomyopathy, and impairment of respiratory function. There are 3 clinical forms of Pompe disease: infantile-, juvenile- and adult-onset forms. Patients with the infantile-onset form have severe cardiomyopathy and muscle weakness, and usually die by 18 months of age from respiratory failure. The frequency of infantile-onset disease is highest in African-Americans 1/14,000 and Chinese 1/40-50,000. The juvenile- and adult-onset forms of Pompe Disease, which are collectively called "late-onset" disease, are more attenuated. Symptoms develop in childhood or early adulthood. Disease progression may extend over years to decades. Glycogen accumulation predominantly affects skeletal muscle. Like patients with infantile onset disease, death is secondary to respiratory failure. The frequency of late-onset disease is approximately 1/60,000 in Caucasian populations.[3]

Alglucosidase alfa is a purified analog of naturally occurring, endogenous lysosomal GAA, produced by recombinant DNA technology developed in a Chinese hamster ovary (CHO) cell line. After intravenous administration, alglucosidase alfa is internalized by cells via cell membrane mannose-6-phosphate receptors that bind to enzyme mannose-6-phosphate residues. Intracellularly, the enzyme is taken up by lysosomes and undergoes proteolytic cleavage, which increases its enzymatic activity. The product must be internalized intracellularly to function as intended, so the impact of its biochemical characteristics on its ability to interact with cell membrane mannose-6-phosphate receptors has been a critical review issue.

This BLA has been subject to more than one CR action and the product that will be marketed, Lumizyme 4000 L, was not the original bioreactor scale product (2000 L) submitted in the initial BLA submission. In this section of my review, I will present an overview of the highlights of the regulatory history of this BLA starting at the time of its initial submission, as subsections below based on the dates of Genzyme's BLA submissions: the May 30, 2008 initial BLA submission, the May 15, 2009 complete response, and the current December 16, 2009 complete response.

Initial BLA Submission Lumizyme 2000L May 30, 2008

The original BLA submission for Lumizyme 2000 L was dated May 30, 2008. The Applicant's proposed indication was for the treatment of non-infantile-onset Pompe disease. The BLA was granted a priority review and was discussed at a closed and an open session of the Endocrinologic and Metabolic Drugs Advisory Committee meeting on October 21, 2008. In the closed session the differences in production and biochemical characteristics between Myozyme (alglucosidase alfa 160 L) and Lumizyme 2000 L were presented. The potential impact of the biochemical differences on the relative safety and efficacy of Lumizyme 2000 L were discussed. The reviewers were concerned that the differences in critical product

[3] 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

attributes in the larger scale product, Lumizyme 2000 L, could result in decreased efficacy, which could be devastating if used for the most aggressive phenotypes of Pompe disease.

The efficacy outcomes observed in the single placebo-controlled trial were discussed in the AC open session. The Committee did not believe that the trial (LOTS) had established a favorable effect of Lumizyme 2000 L on the primary endpoint, 6-minute walk test. However, the committee voted 16 to 1 in favor of accelerated approval (21 CFR 601.41-46 (Subpart E)) of Lumizyme 2000 L based on a surrogate endpoint reasonably likely to predict clinical benefit, percent of predicted forced vital capacity (FVC), for treatment of patients with late (non-infantile) onset Pompe disease, ages 8 years and older, who do not have evidence of cardiac hypertrophy.

A complete response (CR) action was taken on February 27, 2009, and a Warning Letter was issued by the FDA's Office of Compliance on the same date for CGMP deficiencies identified during FDA's October 2008 inspection of the Allston Landing, MA manufacturing facility. The Office of Compliance had recommended "Withhold" approval on February 6, 2009. The CR letter stated the following issues must be addressed: 1) CGMP deficiencies identified in the inspection of the Allston Landing, MA manufacturing facility, 2) CMC deficiencies in the BLA, 3) the design of a post-approval study to be conducted under 21 CFR 601.41-46 (Subpart E) to verify the clinical benefit of Lumizyme 2000 L, and 4) a revised REMS.

Post CR Action Letter Activities: The Division of Gastroenterology Products (DGP) and Genzyme met to determine the optimal design for the post-approval study to verify the clinical benefit of Lumizyme (2000L). Lumizyme (2000L) has been approved and marketed outside the U.S. and Genzyme maintains a multi-national, observational Pompe Registry. DGP asked Genzyme to identify and submit data from the Pompe Registry on patients with infantile-onset disease who had been treated with Lumizyme because these data might provide evidence of clinical benefit. Myozyme was approved based on a comparison to a historical control of 61 patients with infantile onset disease diagnosed by age 6 months, born between 1982 and 2002. By age 18 months only one of the 61 historical control patients was alive (98% mortality). DGP asked that Genzyme identify Pompe Registry patients who had been treated with Lumizyme (2000L) prior to 6 months of age who could be matched to the previous historical control used for the Myozyme BLA. Evidence of improved survival in these matched patients from the Pompe Registry could establish the clinical benefit of Lumizyme (2000l).

Complete Response Submission May 15, 2009 (Lumizyme 2000L)

Genzyme responded to the CR letter on May 15, 2009. The Allston Landing facility was re-inspected in May 2009, October 2009 and November 2009. Several deficiencies were identified on inspection and on November 6, 2009, the Office of Compliance again recommended withholding approval of the BLA. Another CR letter was issued on November 13, 2009, in keeping with the recommendation of the Office of Compliance.

The non-CGMP issues identified in the previous February 27, 2009 CR letter were adequately addressed in this submission. Genzyme submitted data in this Complete Response from 15

infantile-onset patients enrolled in the Pompe registry who had received Lumizyme 2000L prior to 6 months of age. These patients were matched to the untreated historical control group that was analyzed to support Myozyme's approval. The median duration of Lumizyme 2000 L treatment in the 15 Pompe Registry patients was 15 months (range 3-48 months) and the estimated survival was 57% at 18 months and 37% at 36 months (compared to the 2% survival in the historical control). The reviewers concluded that these data supported the findings of the LOTS trial and provided the necessary evidence of clinical benefit of Lumizyme 2000 L to support regular approval of Lumizyme 2000 L for treatment of patients 8 years and older with late-onset Pompe disease. (b) (4)

A REMS was submitted to address the concerns about the risks of use of Lumizyme 2000 L in patients less than 8 years of age, i.e., the potential risk of rapid disease progression in infantile-onset Pompe disease patients and in patients with late (non-infantile) onset disease less than 8 years of age for whom the safety and effectiveness of Lumizyme 2000 L have not been evaluated. In addition, a REMS is necessary to ensure that the known risks of anaphylaxis and severe allergic reactions associated with the use of Lumizyme 2000 L and the potential risks of severe cutaneous and systemic immune complex-mediated reactions to Lumizyme are communicated to patients and prescribers.

***Post CR Action Letter Activities*:**

The European Medicines Agency (EMA) approved the 4000 L bioreactor scale of alglucosidase alfa, produced at Genzyme's manufacturing facility in Geel, Belgium in February 2009. From the time of the first May 15, 2009 CR action and Genzyme's submission of a second complete response on December 16, 2009, FDA and Genzyme engaged in multiple discussions regarding the ongoing Allston Landing, MA manufacturing issues (manufacturing site of Lumizyme 2000 L). The FDA encouraged Genzyme to submit CMC information on Lumizyme 4000 L for evaluation under IND 10,780 (alglucosidase alfa 2000 L), because Lumizyme 4000 L is produced in their Geel, Belgium facility, not in Allston Landing, MA. Upon preliminary review of the product data for the 4000L product, the DTP reviewers determined that the 4000 L product appeared sufficiently comparable to the 2000 L product that it would be possible to formally review the 4000 L product in a response to the CR letter.

Based on this determination by DTP, the FDA agreed that manufacturing information and product quality information for the 4000 L bioreactor scale product could be submitted as part

of the second Complete Response submission, and if the final review established that there is sufficient biochemical comparability between the 2000 L and 4000 L products, no additional clinical information would be required (with the exception of a safety update). Furthermore, if the Geel, Belgium facility was found acceptable on inspection, and the 4000 L product was found to be acceptably comparable to the 2000 L product, the BLA for marketing the 4000 L product from the Geel, Belgium facility could be approved since it is not manufactured, filled or finished at the Allston Landing, MA facility.

Complete Response Submission December 16, 2009 (Lumizyme 4000 L)

The DTP reviewers determined in this review cycle that Lumizyme 4000 L demonstrates sufficient comparability in critical product quality attributes to Lumizyme 2000 L. During the previous review cycle, the clinical reviewers determined that the Applicant had provided substantial evidence of efficacy and safety to support approval of Lumizyme for the indication treatment of patients 8 years and older with late (non-infantile) onset Pompe disease [α-glucosidase (GAA) deficiency] who do not have evidence of cardiac hypertrophy. Persistent manufacturing site deficiencies at the Allston Landing facility had previously precluded approval of Lumizyme 2000 L. However, with the establishment of sufficient physicochemical comparability of Lumizyme 4000 L with Lumizyme 2000 L, and the Office of Compliance's determination that the manufacturing site of Lumizyme 4000 L (Geel Belgium) is acceptable, Lumizyme 4000 L can be approved for this indication. The product labeling and REMS have been completed.

I concur with all the review disciplines that this BLA should be approved.

3. CMC

I concur with the product quality reviewers' recommendations for approval of Lumizyme 4000 L for the proposed indication. They found that the data provided for review in the current BLA submission establish physicochemical comparability between Lumizyme 4000 L and Lumizyme 2000 L and that there are improvements in the Lumizyme 4000 L product in a number of critical attributes. The reviewers concluded that the manufacture of Lumizyme 4000 L 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. I concur with their recommendations for post-marketing commitments.

The Office of Compliance, Division of Manufacturing and Product Quality (DMPQ) has also recommended approval of Lumizyme 4000 L. I agree with their recommendations for post-marketing commitments.

The CDTL review thoroughly documents the CMC review issues from each review cycle. I will briefly list the major issues, by review cycle, below:

A. Product Quality Review

Initial BLA Submission Lumizyme 2000L May 30, 2008

Differences in critical product attributes were identified between the Myozyme (160 L) and Lumizyme 2000 L products that could cause differences in potency and immunogenicity. (b) (4) Additional concerns/deficiencies included:

1. Cell viability is a critical parameter for controlling product quality during (b) (4) The BLA lacked adequate justification for not using cell viability as an in-process control for bioreactor monitoring.

2. An established reference standard for use in the testing control strategy that is representative of the 2000 L process was not submitted. Data were needed to support the qualification of a reference standard.

3. The acceptance criteria for drug substance and drug product specifications were not consistent with manufacturing process capability. The Applicant was asked to provide an evaluation of the following analytical tests: (b) (4) assay; SDS-PAGE gel assays; HPLC for measurement of total mannose-6-phosphate (M6P); HPAEC-PAD for measurement of (b) (4) profiling; and size exclusion chromatography.

4. The Applicant was asked to revise the criterion used for the system suitability requirement regarding the precision of the (b) (4) assay to better reflect assay performance.

Applicant's Complete Response Submission May 15, 2009 (Lumizyme 2000L)

The Applicant's Complete Response addressed all the CMC deficiencies identified in the first Complete Response Letter. The Applicant 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.

Applicant's Complete Response Submission December 16, 2009 (Lumizyme 4000 L)

In this review cycle the product quality reviewers evaluated the physicochemical comparability of Lumizyme 2000 L and Lumizyme 4000 L. They evaluated whether manufacturing process changes to produce Lumizyme 4000 L impacted critical product quality attributes. The reviewers noted that the cell culture process for Lumizyme 4000 L is the same as the Lumizyme 2000 L process, with the exception of the (b) (4), which did not result in a change in genetic integrity of the cells. There was no evidence of contamination or recovery of adventitious agents. The reviewer identified two major changes in purification of rhGAA in the 4000 L process and the impact on the 4000L product:

(b) (4)

The reviewer found the overall validation of the purification process adequate. He recommended addition of a (b) (4) assay to the testing program.

Drug Substance. The proposed drug substance specifications for Lumizyme 4000 L differed from Lumizyme 2000 L for a number of critical product quality attributes, (b) (4)

Other critical product quality attributes that differed (between Lumizyme 4000 L and Lumiyzme 2000 L) were (b) (4)

With regard to other product quality attributes, there was (b) (4)

Stability. The Lumizyme 4000 L and Lumizyme 2000 L drug substances degrade in response to pH and temperature at similar rates. The Lumizyme 4000 L and Lumizyme 2000 L drug products had similar stability attributes. (b) (4)

Product Quality Reviewers Recommendations for Post-Approval Studies-

The reviewers recommended 11 post-marketing commitment studies, which can be found listed at the end of this review in Section 13. These studies were recommended to further characterize and validate the 4000 L production processes and will be performed post-approval, due to the current drug shortage. The Deputy Director and Director of Division of Therapeutic Proteins concurred with this recommendation. The studies were not considered critical to the approval of Lumizyme 4000L product.

B. Manufacturing Site Inspection

Initial BLA Submission Lumizyme 2000L May 30, 2008

Lumizyme 2000 L is manufactured at the Applicant's Allston Landing, MA facility. Inspection of that facility detected deviations from current Good Manufacturing Practices (CGMP) that were cited in an FDA Form 483 issued on October 10, 2008. The Applicant's response to these deficiencies was not adequate, and a Warning Letter was issued by the Office of Compliance on February 27, 2009. The following deficiencies were cited:

1. Failure to establish and follow written procedures designed to prevent microbiological contamination of drug products
2. Failure to assure there are written production and process controls designed to assure 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 manufacture, processing, packaging or holding.
4. Failure to maintain computerized systems in a validated state.

The Office of Compliance recommended a Withhold approval action. A complete response (CR) action was taken on February 27, 2009.

During the first review cycle, on November 14, 2008, there was a 2000 L bioreactor crash (i.e., rapid cell death) at the Allston Landing, MA facility. Another bioreactor crash occurred in May 2009 at the same facility. The Applicant determined that bioreactor crash was secondary to viral contamination with Vesivirus 2117 and concluded raw materials were the likely source of contamination.

Applicant's First Complete Response May 15, 2009 (Lumizyme 2000L)

The Allston Landing, MA facility was re-inspected in May 2009. The Applicant had not instituted full corrective actions in time for that re-inspection, so another re-inspection was conducted in October. In October 2009, the Applicant reported a new issue at the facility: contamination of intravenous drug products (including Lumizyme 2000 L) with foreign particulate matter (stainless steel, rubber stopper particles, human hair, cellulosic fibers, and blue fibers). Inspectors determined the facility did not comply with requirements set forth in the 21 CFR 601.20 (a) and (d). The New England District Office updated the firm's GMP profile to "further action indicated." The Applicant's CGMP profile continued to be classified

as Official Action Indicated (OAI). The Office of Compliance recommended a Withhold approval action for this BLA on November 6, 2009.

Applicant's Complete Response December 16, 2009 (Lumizyme 4000 L)

The manufacturing information for Lumizyme 4000 L was submitted to the BLA to address the deficiencies cited in the second Complete Response Letter. The Applicant withdrew the request for licensure of the Allston Landing, and changed the manufacturing site for the Lumizyme BLA to the Genzyme Flanders and Waterford facilities, where Lumizyme 4000 L is manufactured. The Waterford, Ireland facility had been inspected from October 21-30, 2009, and the Genzyme Flanders facility had been inspected from September 21-29, 2009. Both manufacturing facilities were in compliance with CGMP requirements. Alternate testing sites for the drug substance and drug product include Genzyme Corporation in Framingham, MA and Allston, MA laboratories, which have an acceptable compliance status.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewer concluded that there are no outstanding pharm/tox issues that preclude approval. I concur.

The reviewers in the initial review cycle were not convinced by the nonclinical data presented in the BLA that suggested Lumizyme 2000 L produced similar glycogen clearance relative to Myozyme. They expressed concern that the glycogen clearance assays were insufficiently sensitive to establish comparability between the products. Two nonclinical studies suggested that glycogen clearance activity was directly correlated with mannose-6-phosphate receptor binding affinity.

5. Clinical Pharmacology

I concur with the clinical pharmacology reviewers that there are no clinical pharmacology issues that preclude approval. They recommended that additional PK data be collected in Pompe patients ages 8 to 18 years to further characterize the PK profile in pediatric patients, utilizing Lumizyme 4000 L, as a post-marketing commitment. I agree.

In the initial submission of this BLA the Clinical Pharmacology reviewers evaluated the multiple-dose pharmacokinetic (PK) data for Lumizyme 2000 L. Pharmacokinetics were studied in 32 patients with late-onset Pompe disease, in the LOTS efficacy trial. The PK parameters (Cmax, AUCinf, clearance, Vss, and effective half life) appeared comparable over time, measured at Weeks 0, 12, and 52.

With regard to immunogenicity, all patients treated with the 2000 L product in the LOTS efficacy trial tested positive for anti-rhGAA IgG antibodies as assessed by enzyme-linked immunosorption assay (ELISA) and confirmed by radio-immunoprecipitation assay (RIP). Median time to seroconversion was 4 weeks. There was some evidence of decreasing titers with continued treatment; however, 9/59 patients (15%) who developed positive IgG titers had

persistent elevation at study end. None of the IgG positive patients tested positive for inhibition of enzyme activity; however, there was evidence of inhibition of cellular uptake into fibroblast cells in 10 patients who tested "positive" and 8 who tested "borderline positive." The presence of both high anti-rhGAA IgG antibody titers and positive inhibitory antibody status appeared to affect product pharmacokinetics, resulting in an apparent higher clearance, lower Cmax and lower AUC. Data were considered inconclusive to determine whether inhibitory or high IgG antibodies were actually responsible for the observed increased clearance. In fact, efficacy data suggested a trend towards greater improvement in the 6 minute walk test (6MWT) in the presence of higher IgG titers and, possibly, positive inhibitory antibody status. There was no association between anti-rhGAA IgG titers and infusion reactions.

Because the 4000 L product demonstrated sufficient physicochemical comparability with the 2000 L product based on critical product quality attributes, and because the change in manufacturing process between the 2000 L and 4000 L production scales was not considered a major manufacturing process change, additional clinical pharmacology data to establish the comparability of the 4000 L and 2000 L production scales were not required.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

I concur with the reviewers and the CDTL that the clinical efficacy information submitted from the original BLA submission (LOTS) and the first complete response submission (Pompe registry) provide substantial evidence of the effectiveness of Lumizyme in the treatment of late-onset Pompe disease. I agree with their conclusion that limitations in the Pompe Registry data support a cautious approach to defining the population for which Lumizyme should be indicated. Patients with more rapidly progressive disease, i.e. infantile-onset Pompe disease, patients with cardiac hypertrophy and children diagnosed at an age <8 years, should be treated with Myozyme. Lumizyme should be indicated only for patients with late-onset Pompe patients 8 years of age and older who do not have cardiac hypertrophy. The difference in the Lumizyme indication from that of Myozyme is particularly relevant in light of important physicochemical differences between Myozyme and Lumizyme that may result in decreased potency of Lumizyme. These important differences support that the products are different products and that they should not be used interchangeably. The physicochemical comparability between Lumizyme 2000 L and Lumizyme 4000 L was established by the product quality reviewers, and Myozyme and Lumizyme 4000L are also not interchangeable. Based on the important physicochemical differences between the Myozyme and Lumizyme and the limitations of the Pompe Registry data, the CDTL has recommended a risk evaluation and mitigation strategy (REMS) be required 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. I concur with this recommendation.

The efficacy and safety of Lumizyme 2000 L were studied in a multicenter randomized, double-blind, placebo-controlled trial that enrolled patients with late-onset Pompe disease. Enrollment in the trial, Late-Onset Treatment Study or LOTS, 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, using a computerized minimization algorithm for randomization rather than blocked randomization, to either 20 mg/kg of the 2000L product administered intravenously every two weeks or placebo. Ninety patients were studied.

The original design was a 52-week trial with co-primary endpoints: 1) distance walked during the six minute walk test (6MWT) at 52 weeks, adjusted for the baseline, and 2) upright percent of predicted forced vital capacity (FVC) at 52 weeks, adjusted for the baseline. The statistical plan stated that the 6MWT was to be examined first and if the effect was statistically significant, the percentage of predicted FVC could be evaluated. While the study was ongoing, the design was changed to an adaptive strategy in order to determine, through interim analysis, the optimal duration of the study, and to compare the trial arms over the course of the study rather than focusing on the comparisons at 52 weeks. This strategy resulted in extending the trial duration from 52 weeks to 78 weeks. Changes were also made in the primary endpoint definitions.

Among the trial design changes that occurred during study conduct was a decision to use a linear effects model for the primary efficacy analysis, which assumed that the 6MWT and FVC results would change linearly over time. When the data were analyzed, tests determined the 6MWT departed from the assumptions of both linearity and normality. As a result, the Applicant proposed the use of a "sandwich" estimator of the variance-covariance matrix. The statistical reviewer agreed that the "sandwich" estimator is more appropriate; however, its use left some unanswered questions. The statistical reviewer noted that if the results had been statistically significant, the Applicant would likely not have explored use of the "sandwich" estimator. The Applicant also included results from other analyses that were not pre-specified (i.e., generalized estimating equation (GEE) models and non-parametric assessments of the data). These tests gave statistically significant results for the 6MWT. However, the statistical reviewer questioned the use of models that were not prespecified.

The Statistical reviewer noted that in the setting of randomization by minimization algorithm, appropriate statistical analysis should include re-randomization testing. She noted that results from re-randomization tests are usually similar to the result from classical testing procedure, but found that this was not true for the LOTS efficacy analysis. The p-value shifted substantially in the ANCOVA analysis of the 6MWT when re-randomization was applied (p-value changed from 0.035 to 0.06).

Therefore, the statistical reviewer concluded that because of the violations of the assumptions underlying the linear mixed effects model and the changes to the model after the data were unblinded, the results of the ANCOVA with re-randomization testing should be emphasized. The statistical reviewer noted that the ANCOVA was consistent with the clinical question of

interest, which was whether the change from baseline to the last observation differs between 2000L-treated patients and placebo-treated patients.

The ANCOVA analysis of the 6MWT is summarized in the table below, which is reproduced from the CDTL review. The difference between arms was not statistically significant, p=0.06.

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

	2000 L N=60	Placebo N=30	Difference
Summary statistics:			
Mean (±SD) distance walked at baseline	332.2 (128.0)	314.06 (131.4)	n/a
Mean (±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
Results of ANCOVA:*			
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)

The ANCOVA analysis of the results for the co-primary endpoint FVC (which technically was only to be evaluated if the 6MWT analysis was statistically significant) is summarized in the table below, also reproduced from the CDTL review.

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

	2000 L N=60	Placebo N=30	Difference
Summary statistics:			
Mean (± SD) FVC at baseline	55.58 (14.5)	53.36 (15.4)	n/a
Mean (± SD) change from baseline to last observation in FVC	1.37 (5.0)	-1.82 (4.4)	3.19
Results of ANCOVA:*			
Mean (± 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)

This BLA application was presented to Endocrinology and Metabolic Drugs Advisory Committee (EMDAC) on October 21, 2008. Although the Committee voted 16-1 that the effectiveness of the 2000 L product had been demonstrated in LOTS, twelve Committee members recommended that the product should be granted accelerated approval under Subpart E, based on the data for the endpoint FVC, an endpoint considered to be a surrogate

reasonably likely to predict clinical benefit. Accelerated approval regulations require that an Applicant perform a verification study to confirm the clinical benefit of the 2000 L product. The Committee unanimously voted to require post-marketing safety studies to address concerns of anaphylaxis, immunogenicity, and potential chronic immune-mediated reactions. Committee members recommended that a REMS be required to ensure the safe use of the 2000 L product.

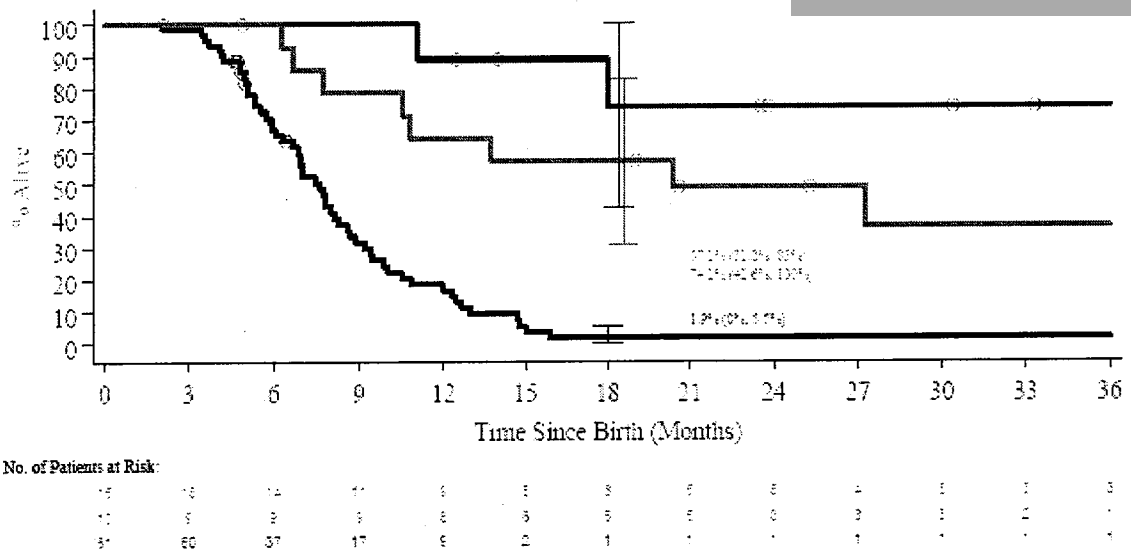
The Agency was unable to approve the product in the first cycle because of serious manufacturing deficiencies identified in the inspection of the Allston Landing, MA manufacturing facility and CMC deficiencies in the BLA. The Applicant and FDA had also not reached agreement on the design of the post-approval study to be conducted under Subpart E accelerated approval regulations to verify the clinical benefit of Lumizyme, and a revised REMS had not been submitted. The Agency and the Applicant engaged in multiple discussions after the initial CR action, and came to an agreement that additional clinical information (i.e. outcomes data) from the Pompe Registry, (a multinational disease registry established in response to a post-marketing commitment that was a condition for the 2006 approval of Myozyme), may provide sufficient clinical outcome information to support regular approval for the 2000 L product, instead of approval under Subpart E. The Applicant submitted clinical outcomes data in patients treated with Lumizyme 2000 L from the Pompe Registry in their initial response to the first CR letter dated February 27, 2009.

The primary objectives of the Pompe Registry, which is a voluntary registry, were to evaluate the long-term effectiveness and safety of available treatment options and to enhance the understanding of the natural history of Pompe disease. The data collected include standard of care clinical assessments determined by the patient's physician, and 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 enzyme replacement therapy (ERT), and neuro-imaging studies. Long-term clinical outcomes such as survival and ventilator-free survival are collected. The Registry includes both prospectively and retrospectively collected data.

The Applicant submitted data from the Pompe Registry comparing the survival and ventilator-free survival outcomes of a subset of infantile-onset Pompe patients who had been treated exclusively with Lumizyme 2000 L to an age- and diseased-matched historical control. Infantile-onset patients generally have a rapidly progressive form of the disease, which enables definitive outcome comparisons to be conducted over a relatively short period of time, an 18 to 24 month period. There were 48 patients enrolled in the Pompe registry who met the inclusion criteria for this analysis. Only 25 of these patients had not been previously studied or reported by the Applicant, and had received either Lumizyme 2000 L exclusively (ex-US infantile-onset patients) or Myozyme (160L product, US infantile onset patients). Of these 25 patients, 10 were US patients who had received Myozyme and 15 were ex-U.S. patients treated with Lumizyme 2000 L exclusively. The median duration of treatment, median age at first infusion, and median age at death or last follow-up were similar between these two groups.

Comparisons were made to the data from natural history studies in infantile-onset Pompe disease, in which only 3% of patients survived past the age of 18 months, and between the two

Pompe Registry groups (Myozyme vs. Lumizyme 2000 L). The Kaplan-Meier estimate of survival at 18 months demonstrated a difference in survival for both Myozyme and Lumizyme 2000 L relative to the historical control group (see Figure 1 below, which is reproduced from the CDTL review). The sample size is limited but the 95% confidence intervals for the treated groups do not overlap with the historical control group. One of the 15 patients treated with the 2000 L product and 3/10 Myozyme-treated patients were alive but had not yet been followed out to18 months of age.



The reviewers were persuaded that these data demonstrated an increase in survival at 18 months in both the Lumizyme 2000 L and Myozyme treatment groups compared with the historical control. The Clinical reviewer noted that there also seemed to be improved survival associated with Myozyme treatment relative to Lumizyme 2000 L; however, the reviewers recognized that the small number of patients precluded drawing definitive conclusions regarding relative efficacy of the two products in patients with infantile-onset Pompe disease.

The Applicant also presented immunogenicity and cross-reacting immunologic material (CRIM) status from the registry population; however, only 17 of the 25 patients had antibody information reported. The paucity of information made it impossible to evaluate the effect of immunogenicity on either safety or efficacy in this population. CRIM status was available in 16/25 patients. Overall survival in CRIM negative patients was 20% (1/5 patients) in the group treated with Lumizyme 2000 L, whereas 100% of CRIM negative patients in the Myozyme treated group were alive. Four of the 10 patients who died while being treated with Lumizyme 2000 L were CRIM negative, whereas none of the patients who died in the Myozyme group were. The reviewers thought these data suggest that differences in CRIM status may contribute to the increase in mortality in the Lumizyme 2000 L group, but they acknowledged that the small numbers of patients precluded drawing definitive conclusions.

The reviewers concluded that the Pompe Registry data submitted in the first response to the CR provided substantial evidence of the efficacy of Lumizyme 2000 L and supported

full/regular approval of Lumizyme 2000 L. (b) (4)

Establishment of efficacy of Lumizyme 4000 L relies on the physicochemical comparability between Lumizyme 2000 L and Lumizyme 4000 L. No additional clinical studies were submitted in support of the clinical effectiveness of Lumizyme 4000 L.

8. Safety

The CDTL concluded that the safety information provided in this BLA on Lumizyme 2000 L, combined with the product quality reviewers' assessment that Lumizyme 4000 L is comparable in critical product quality attributes to Lumizyme 2000 L, is adequate to support an appropriate risk/benefit analysis. I agree with the CDTL and concur that the safety dataset supports approval. There were no clinical trial safety data submitted on Lumizyme 4000 L, but the comparable quality attributes support approving the product on the basis of the clinical safety data submitted from study of Lumizyme 2000 L. Anaphylaxis and infusion reactions are important safety concerns, as well as the potential for chronic immune-mediated (e.g., skin and kidney) adverse reactions. These safety issues warrant a boxed warning in product labeling and implementation of a Risk Evaluation and Mitigation (REMS) 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. There will be post-marketing requirement and commitment studies to evaluate the long-term safety and effectiveness of Lumizyme in patients with late-onset Pompe disease.

The major source of safety information in this BLA was the LOTS trial, a placebo-controlled study of Lumizme 2000 L. Additional supportive safety data sources were 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. Overall, the Applicant estimated that approximately 823 patients had received the 2000 L product, either in clinical trials and/or the postmarketing setting.

One death occurred in the LOTS efficacy trial. The patient was a 33 year-old woman who died of brain stem ischemia secondary to basilar artery thrombosis, which is a known

complication of Pompe disease. The Reviewer concluded that the death was not related to treatment with Lumizyme 2000 L.

Nine patients dropped out of LOTS (n=4 in the placebo group, and n=5 in the 2000 L product-treated group). In the 2000 L group, one patient died, as described above, two discontinued due to infusion reactions (serious adverse events, anaphylaxis), one dropped out for personal reasons and another to receive commercial product. In the two patients who withdrew due to anaphylaxis, one had laboratory confirmation of IgE mediated anaphylaxis, and the other developed severe angioneurotic edema after the third dose of Lumizyme 2000 L.

There were 27 serious adverse events (SAEs) in 19 patients in LOTS. The SAEs that occurred at a higher incidence in the Lumizyme 2000 L group relative to 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.

In the LOTS safety database, there were 4 cases of anaphylaxis in patients treated with Lumizyme 2000L (incidence of anaphylaxis in the 2000L arm 4/59, or 6.7 %), compared to no cases in the placebo arm. Anaphylaxis and severe allergic reactions have been observed up to 3 hours after infusion of Lumizyme 2000 L. Infusion reactions were the most common adverse reaction. These reactions were reported as anaphylaxis, urticaria, diarrhea, vomiting, dyspnea, rash, hematuria, and chest discomfort. Delayed infusion reactions, occurring up to 48 hours after the infusion, were described as urticaria, dizziness, musculoskeletal weakness and pain. Potential immune-mediated adverse reactions involving skin and kidney were also identified by the reviewers.

Review of the safety data from interim analysis of the LOTS extension study, the Myozyme temporary access program (MTAP), and the Applicant's post-marketing pharmacovigilance database revealed no significant qualitative differences from the safety profile observed in LOTS. The LOTS extension study was an open-label, extension study for LOTS that included 81 patients. Twenty-six patients previously randomized to placebo started treatment with Lumizyme 2000 L in this extension study. Of 176 patients enrolled in MTAP, 52 patients had previously been enrolled in either LOTS or LOTS extension.

In this overall safety dataset, there were a total of 24 deaths (as of a March 16, 2009 cutoff). None occurred in the LOTS extension. Twenty-one were post-market reports, and of those, 14 were patients with infantile-onset disease. The most common cause of death was cardiac or respiratory failure.

Five new SAEs in 3 patients were reported in the LOTS extension. They included cervical carcinoma, nephrolithiasis, renal cyst, and gastric ulcer and were not considered treatment related. An additional 28 SAEs reported in 8 patients from MTAP, and 54 post-marketing reports of SAEs in 17 late-onset patients were characterized as infusion reactions (urticaria, facial edema, fever, irritability, decreased oxygen saturation, and tachypnea). Anaphylaxis, pneumonia, respiratory and cardiac failure were reported. In the review of adverse events from the LOTS extension, two additional patients were considered by the reviewer to have had

anaphylaxis that was not reported as an SAE. In MTAP there were 3 patients with signs and symptoms consistent with anaphylaxis.

In the current submission, the most recent response to the last CR letter, the Applicant submitted safety data from the Aglucosidase alfa Temporary Access Program (formerly MTAP), an expanded access program designed to provide treatment to adult Pompe patients in the U.S. pending approval of the 4000 L product. Patients in this program began treatment with Lumizyme 4000 L in October 2009. Only 128 patients received at least one infusion of the product 4000 L product in the Temporary Access program. The maximum exposure was three doses over a 6 week period. The majority had previously received Lumizyme 2000 L prior to Lumizyme 4000 L. Clear differences in the safety profile between product scales could not be identified. There were no deaths and there was 1 SAE (hospitalization for vomiting and diarrhea attributed to viral gastroenteritis). There were no reports of anaphylaxis, skin, kidney or other potentially immune-mediated adverse events. There was one infusion reaction.

The Applicant also submitted Lumizyme 4000 L safety data obtained from the ex-U.S. postmarketing reporting. Lumizyme 4000 L has been marketed outside the US since March 2009. Data were provided for the period from December 29, 2008 to November 24, 2009. Approximately (b) (4) patients were estimated to have received at least one dose of Lumizyme 4000 L during this period. The Applicant reported 7 patient deaths (all ex-U.S.) during treatment with Lumizyme 4000 L (4 patients with infantile-onset, and 3 patients with late-onset). Deaths were attributed to underlying disease. A total of 70 SAEs were reported in patients receiving Lumizyme 4000 L (anaphylaxis, infusion reactions, respiratory distress, pneumonia, septic shock, cough, and respiratory disorder). These did not qualitatively differ from SAEs that have been reported with Lumizyme 2000 L. There were no reports of immune complex-mediated reactions involving the skin or kidneys.

9. Advisory Committee Meeting

As described earlier in Sections 2 and 7 of this review, an Advisory Committee was convened on October 21, 2008, during the first review cycle of this BLA, to discuss the CMC/product quality issues of Lumizyme 2000 L (closed session) and to discuss the efficacy and safety data from the LOTS trial (open session). The EMDAC voted 16 to 1 to approve Lumizyme 2000 L, but the majority recommended approval under Accelerated Approval (21 CFR 601.41-46 Subpart E), based on improvement in percentage predicted FVC, which was considered a surrogate marker, reasonably likely to predict clinical benefit. The Committee recommended requiring post-marketing safety studies to address the concerns of anaphylaxis, immunogenicity, and potential chronic immune-mediated reactions. Committee members recommended that a REMS be required as a condition of approval.

10. Pediatrics

Aglucosidase alfa was designated Orphan Status in 1997. PREA does not apply to products with Orphan Status.

11. Other Relevant Regulatory Issues

Financial Disclosures: Financial disclosures were submitted by the Applicant during the first review cycle. The CDTL reports that there were "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 (b) (6). Another investigator for a U.S. transfer site (b) (6) received royalties and payments upon FDA approval of Myzoyme of $7,914,895 and an additional $468,715 in grants, retainers, honoraria, and retainers from (b) (6)." She concluded that despite these financial relationships, " ...conduct of the studies does not appear to have been affected..."

DSI: Three clinical sites were inspected (Erasmus Medical Center, the Netherlands; Sophia's Children Hospital, the Netherlands; Tower Hematology Oncology Medical Group, U.S.). The DSI inspector found that the sites' data are reliable and can be used in support of the BLA.

Drug Shortage Issues: The CDTL provides a thorough summary of the drug shortage issues that occurred before the submission of this BLA and continued during the review. She noted that there has been a Myozyme drug shortage since 2007 caused by "manufacturing constraints, 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." Approval of Lumizyme should eliminate the current US drug shortage for patients with Pompe disease.

In light of the shortages, Myozyme (160 L) has been reserved for infants and children up to 18 years of age. The Applicant made the 2000 L scale product available under the expanded access program, Myozyme Temporary Access Program (MTAP) to only those adult Pompe patients who are wheelchair bound or require ventilatory assistance. The Applicant closed new enrollment to MTAP in April, 2008. This left US patients with late-onset Pompe disease who were not already on MTAP without access to treatment.

In August, 2009, the Applicant submitted an amendment to MTAP to allow administration of Lumizyme 4000 L to patients already enrolled, in order to conserve Lumizyme 2000 L supply pending the anticipated approval of the Lumizyme 2000 L product in November 2009. The name of the protocol was also changed to Alglucosidase alfa Temporary Access Program (ATAP). The protocol amendment did not allow enrollment of new patients.

After discussions between Genzyme and the FDA Commissioner in August and October, 2009, Genzyme agreed to allow new patients who met enrollment criteria to enter ATAP, i.e., patients who are wheelchair-bound or requiring ventilatory assistance. Although the Agency recommended broadening the enrollment criteria for ATAP to include all patients for whom their treating physician determines medical need, the Applicant did not do so.

12. Labeling

Please see the CDTL reviewer's detailed description of the labeling issues. I will briefly identify the major issues in my review.

Proprietary Name: The Applicant proposed the trade name "Myozyme" for the 2000 L product in the original BLA submission. "Myozyme" has been in use for the 160 L product since its approval in 2006. DMEPA expressed concern over the potential for name confusion that could lead to medication errors. The Applicant proposed the name "Lumizyme," which DMEPA found acceptable. Upon multiple re-reviews, this name remains acceptable.

Package Insert/Physician labeling:

1. 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. It 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. The intent of this language is to warn prescribers about the serious known risks of Lumizyme and to warn prescribers that Lumizyme is only available through a restricted distribution program because of the potential risk of rapid disease progression in infantile-onset patients and patients less than 8 years of age. These patients should continue to be treated with Myozyme.

2. The **Indication** is limited 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** include information regarding the most serious adverse reactions associated with Lumizyme (anaphylaxis, severe allergic and immune-mediated reactions, risk of acute cardiopulmonary failure) and information regarding the restricted distribution program. Information is provided on the Lumizyme ACE Program. There are precautions about the need to monitor anti-rhGAA antibody levels while receiving Lumizyme.

4. **Use in Specific Populations: Pediatric Use** informs prescribers 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. Labeling does not explicitly state that Myozyme is available for infantile-onset Pompe patients and late-onset Pompe patients ages 8 years and younger.

5. The **Description** section includes information that Myozyme and Lumizyme are produced using different manufacturing processes, but it stops short of describing the differences between the two products in critical product attributes that may cause differences in potency.

6. **The Clinical studies** section cites data from the controlled study LOTS and the information from the Pompe Registry that were used to establish the clinical effectiveness of Lumizyme.

7. **Patient Counseling Information** includes a list of information for prescribers to provide to patients, including information on the Lumizyme ACE Program, the Pompe Registry, and the most common adverse reactions associated with Lumizyme (i.e., infusion reactions).

8. A **Medication Guide** was not considered necessary because patients are treated in specialized infusion centers under the supervision of trained personnel.

9. The **Dosage and Administration** section includes language that an in-line filter should be used in administration of the product.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Approval

I concur with the reviewers that the Applicant has provided substantial evidence of efficacy and safety in this BLA to support 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 reviewers have established biochemical comparability between Lumizyme 4000 L and Lumizyme 2000 L based on critical product quality attributes. Therefore, the clinical data that established the safety and efficacy of the 2000L product support the safety and effectiveness of Lumizyme for this indication.

- Risk Benefit Assessment

I agree with the reviewers that while there is sufficient evidence to support the favorable risk/benefit 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, there is cause for concern if Lumizyme is prescribed for patients with more rapidly progressive disease, i.e. infantile onset disease and patients with cardiac hypertrophy, and for patients less than 8 years of age with non-infantile onset disease (since Lumizyme has not been studied in these patients),. Data support the comparability of Lumizyme 4000 L to Lumizyme 2000 L, but data also indicate important differences between Lumizyme 2000 L and Myozyme. The differences in critical product attributes between Lumizyme 2000 L and Myozyme could result in Lumizyme 2000 L being a less potent product and it having a different immunogenicity profile. Both of these differences could negatively impact Lumizyme's safety profile, particularly if it is prescribed for high risk patients with rapidly progressive disease.

I agree with the reviewers that health care providers should be warned of the risks of anaphylaxis and severe allergic reactions, and potential risks of severe cutaneous and systemic immune complex-mediated reactions as listed in the labeling. I agree with the reviewers that Lumizyme cannot be approved without a REMS to assure that the benefits of Lumizyme outweigh the risks of its use.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies - None

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)).

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

The REMS documents can be found appended to the approval letter.

- Recommendation for other Postmarketing Requirements and Commitments
  The following Postmarketing Required Studies will be included in the Approval letter as requirements under Section 505(o) of the Federal Food, Drug, and Cosmetic Act:

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.

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

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

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

In addition, the Applicant has agreed to the following postmarketing commitments subject to reporting requirements of Section 506B:

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

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

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

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

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

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

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

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

Finally, the Applicant has agreed to the following postmarketing commitments that are not subject to reporting requirements of Section 506B:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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