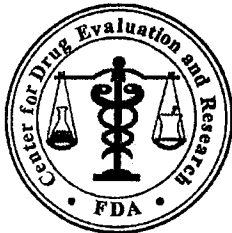


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125291

PROPRIETARY NAME REVIEW(S)



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: March 24, 2010

To: Donna Griebel, MD
Director, Division of Gastroenterology Products

Through: Denise Toyer, PharmD., Deputy Director *DDT 3/24/2010*
Division of Medication Error Prevention and Analysis

From: Zachary Oleszczuk, PharmD, Acting Team Leader *Z 3/24/10*
Division of Medication Error Prevention and Analysis

Subject: Proprietary Name Review

Drug Name(s): Lumizyme (Alglucosidase Alfa) for Injection 50 mg/vial

Application Type/Number: BLA 125291

Applicant: Genzyme Corporation

OSE RCM #: 2009-2422-1

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1 INTRODUCTION

This re-assessment of the proprietary name is written in response to the anticipated approval of BLA 125291 within 90 days from the date of this review. The Division of Medication Error Prevention and Analysis (DMEPA) found the proposed proprietary name, Lumizyme, acceptable in OSE Review #2008-1214, dated November 14, 2008, OSE Review #2009-1030, dated September 9, 2009, and OSE Review #2009-2422, dated December 29, 2010. The Division of Gastroenterology Products did not have any concerns with the proposed name, Lumizyme during any of the previous reviews, and the Division of Drug Marketing, Advertising and Communication (DDMAC) found the name acceptable from a promotional perspective on August 7, 2008, June 4, 2009, December 24, 2009, and March 23, 2010.

2 METHODS

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources (see Section 5) to identify names with orthographic and/or phonetic similarity to the proposed name that have been approved since the completion of the previous OSE proprietary name review. We used the same search criteria outlined in OSE Review #2008-1214, dated November 14, 2008, for the proposed proprietary name, Lumizyme. Since the last review of the proposed proprietary name none of Lumizymes's product characteristics have been altered. Thus, we did not re-evaluate previous names of concern. Additionally, DMEPA searches the USAN stem list to determine if the name contains any USAN stems as of the last USAN updates. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proposed proprietary name, and focuses on the avoidance of medication errors.

3 RESULTS

The searches of the databases did not yield any names that were thought to look or sound similar to Lumizyme and represent a potential source of drug name confusion. Additionally, DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of March 24, 2010.

4 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Lumizyme, is not vulnerable to name confusion that could lead to medication errors, nor is the name considered promotional. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Lumizyme, for this product at this time.

DMEPA considers this a final review; however, if approval of the BLA is delayed beyond 90 days from the date of this review, the Division of Gastroenterology Products should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date.

5 REFERENCES

1. Oleszczuk, Z. OSE Review #2008-1214: Proprietary Name, Label and Labeling Review for Lumizyme. November 14, 2008.
2. Oleszczuk, Z. OSE Review #2009-1030: Proprietary Name Review for Lumizyme. September 9, 2009.
3. Oleszczuk, Z. OSE Review #2009-2422: Proprietary Name Review for Lumizyme. December 29, 2009.

4. ***Drugs@FDA*** (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present.

Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and “Chemical Type 6” approvals.

5. ***USAN Stems*** (<http://www.ama-assn.org/ama/pub/category/4782.html>)

USAN Stems List contains all the recognized USAN stems.

6. ***Division of Medication Error Prevention and Analysis proprietary name requests***

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: December 29, 2009

To: Donna Griebel, MD
Director, Division of Gastroenterology Products

Through: Kellie Taylor, Pharm.D., M.P.H., Team Leader
Denise Toyer, Pharm.D., Deputy Director
Division of Medication Error Prevention and Analysis

From: Zachary Oleszczuk, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Proprietary Name Review

Drug Name(s): Lumizyme (Alglucosidase Alfa) for Injection 50 mg/vial

Application Type/Number: BLA 125291

Applicant: Genzyme Corporation

OSE RCM #: 2009-2422

DPTBperfor 12/29/09

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J 12/29/09

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1 INTRODUCTION

This re-assessment of the proprietary name is written in response to the anticipated approval of BLA 125291 within 90 days from the date of this review. The Division of Medication Error Prevention and Analysis (DMEPA) found the proposed proprietary name, Lumizyme, acceptable in OSE Review #2008-1214, dated November 14, 2008 and OSE Review #2009-1030, dated September 9, 2009. The Division of Gastroenterology Products did not have any concerns with the proposed name, Lumizyme during either previous review on the proposed name, and the Division of Drug Marketing, Advertising and Communication (DDMAC) found the name acceptable from a promotional perspective on August 7, 2008.

2 METHODS

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources (see Section 5) to identify names with orthographic and/or phonetic similarity to the proposed name that have been approved since the completion of the previous OSE proprietary name review. We used the same search criteria outlined in OSE Review #2008-1214, dated November 14, 2008 and OSE Review #2009-1030, dated September 9, 2009, for the proposed proprietary name, Lumizyme. Since the last review of the proposed proprietary name the manufacturing scale of this products has been changed from 2000 liters to 400 liters. This change in manufacturing scale does not alter any of Lumizymes's product characteristics since our previous review. Thus, we did not re-evaluate previous names of concern. Additionally, DMEPA searches the USAN stem list to determine if the name contains any USAN stems as of the last USAN updates. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proposed proprietary name, and focuses on the avoidance of medication errors.

3 RESULTS

The searches of the databases yielded one new name (Zolinza), thought to look similar to Lumizyme and represent a potential source of drug name confusion. However, the findings of the FMEA indicate that the proposed name, Lumizyme, is not likely to result in name confusion with any of the identified names for the reasons presented in Appendix A.

Additionally, DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of December 20, 2009.

4 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Lumizyme, is not vulnerable to name confusion that could lead to medication errors, nor is the name considered promotional. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Lumizyme, for this product at this time.

DMEPA considers this a final review; however, if approval of the BLA is delayed beyond 90 days from the date of this review, the Division of Gastroenterology Products should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date.

5 REFERENCES

1. Oleszczuk, Z. OSE Review #2008-1214: Proprietary Name, Label and Labeling Review for Lumizyme. November 14, 2008.
2. Oleszczuk, Z. OSE Review #2009-1030: Proprietary Name Review for Lumizyme. September 9, 2009.

2. ***Drugs@FDA*** (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present.

Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and “Chemical Type 6” approvals.

3. ***USAN Stems*** (<http://www.ama-assn.org/ama/pub/category/4782.html>)

USAN Stems List contains all the recognized USAN stems.

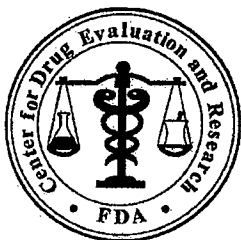
4. ***Division of Medication Error Prevention and Analysis proprietary name requests***

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

APPENDICES

Appendix A: Product with achievable numerical dose but has multiple differentiating product characteristics

Zolinza (vorinostat)	Look	Capsule: 100 mg	400 mg orally once daily	Dosage Form (Powder for injection vs. Capsule) Route (intravenous vs. oral) Dose (20 mg/kg vs. 400 mg) Frequency (every 2 weeks vs. once daily)



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: September 9, 2009

To: Donna Griebel, MD
Director, Division of Gastroenterology Products

Through: Kellie Taylor, PharmD, MPH, Team Leader *Kellie Taylor 9/9/09*
Denise Toyer, Pharm.D., Deputy Director *DP. Toyer 9/10/09*
Carol Holquist, RPh, Director *Carol Holquist 9/10/09*
Division of Medication Error Prevention and Analysis (DMEPA)

From: Zachary Oleszczuk, PharmD, Safety Evaluator *Z 9/9/09*
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Proprietary Name Review

Drug Name(s): Lumizyme (Alglucosidase Alfa) for Injection 50 mg/vial

Application Type/Number: BLA 125291

Applicant/Applicant: Genzyme Corporation

OSE RCM #: 2009-1030

*** This document contains proprietary and confidential information that should not be released to the public.***

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EXECUTIVE SUMMARY

This re-assessment of the proprietary name is written in response to a notification that a regulatory action for BLA #125291 may occur within 90 days. DMEPA found the proposed proprietary name, Lumizyme, acceptable in OSE Review# 2008-1214 dated November 14, 2008. Since that review, none of Lumizyme's product characteristics have changed.

During this re-review DDMAC had no concerns with the name from a promotional perspective and we identified and evaluated 14 new names for their similarity to Lumizyme. The results of the Failure Mode Effects Analysis found that the proposed name, Lumizyme, is not vulnerable to name confusion that could lead to medication errors with any of 14 names. Thus, the Division of Medication Error Prevention and Analysis does not object to the use of the proprietary name, Lumizyme, for this product.

DMEPA considers this a final review, however, if approval of the NDA is delayed beyond 90 days from the date of this review, the Division of Gastroenterology Products should notify DMEPA because the proprietary name must be re-reviewed prior to the new anticipated action date.

1 METHODS AND MATERIALS

Appendix A describes the general methods and materials used by the Division of Medication Error Prevention and Analysis (DMEPA) when conducting a re-assessment of a proprietary name 90 days prior to approval of an application. Section 1.1 identifies the specific search criteria associated with the proposed proprietary name, Lumizyme.

1.1 SEARCH CRITERIA

We used the same search criteria used in OSE Review #2008-1214 date November 14, 2008. Please refer to Section 2.1.1 of that review for the search criteria.

2 RESULTS

2.1 DATABASE AND INFORMATION SOURCES

The searches of the databases listed in Section 6 yielded a total of 15 names as having some similarity to the name Lumizyme.

Twelve of the 15 names were thought to look like Lumizyme. These include Ilozume, Unizyme, Kuzyme, (b) (4) Vegizyme, Cortizyme, (b) (4) Combizyme and Lincomycin. One of the names (Lamisil) was thought to sound like Lumizyme. The remaining two names (Lumizyme and Luminal) were thought to look and sound similar to Lumizyme.

Additionally, DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of June 9, 2009.

2.2 EXPERT PANEL DISCUSSION

The Expert Panel, as described in Appendix A, section 2, reviewed the pool of names identified by DMEPA staff (See Section 2.1 above) and noted no additional names thought to have orthographic or phonetic similarity to Lumizyme.

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name.

2.3 SAFETY EVALUATOR RISK ASSESSMENT

Eleven names (See Appendix B) were identified in the previous Lumizyme proprietary name review. None of Lumizyme's product characteristics have changed since the previous review. Therefore, there was no need to re-evaluate the proposed names as compared to theses name and the original assessment is maintained. Please see OSE# 2008-1214 for a detailed analysis of these names.

For this evaluation, the 15 new names were identified through database searches. One of the 15 names was identified by our database search, however this name is the subject of this review and has been removed from further analysis. Independent searches by the primary Safety Evaluator did not result in any additional names which were thought to look or sound similar to Lumizyme and represent a potential source of drug name confusion. Thus, a total of 14 names were considered.

Two of the 14 names (b) (4) and Ilozume identified by our searches were removed from further evaluation. (b) (4), was previously submitted for this product, but was found unacceptable by the Division of Drug Marketing, Advertising, and Communications (DDMAC) in OSE Review #2008-1214 dated August 11, 2008. For the name Ilozume, we note that attempts to identify the drug product associated with the name Ilozume were unsuccessful. We determined that this name was misspelled during the search process (i.e. Ilozume for (b) (4)). Since (b) (4) was evaluated in the previous review of the name Lumizyme, has not had any changes in product characteristic and was found not to be vulnerable to confusion in the usual practice setting, the name Ilozume was removed from further evaluation.

Additionally, one name, Unizyme, was found to be a proprietary name for two different products. Unizyme is a nutritional supplement and Unizyme is a contact lens cleaner. Since Unizyme is the proprietary name of two different products, this name was evaluated as two separate names. Unizyme [1] is used to designate the nutritional supplement, and Unizyme [2] is used to designate the contact lens cleaner. As such, a total of 13 names were analyzed to determine if the drug names could be confused with Lumizyme and if the drug name confusion would likely result in a medication error in the usual practice setting.

3 DISCUSSION

DDMAC had no concerns with the name from a promotional perspective. The Division of Gastroenterology Products (DGP) did not have any issues with the name. We did not identify any safety issues with the proposed name except for potential look and sound-alike names. Thirteen names were evaluated for their potential similarity to the proposed name, Lumizyme. Five names lacked orthographic and/or phonetic similarity and were not evaluated further (see Appendix C).

Failure mode and effect analysis (FMEA) was then applied to determine if the proposed name could potentially be confused with the remaining eight names and lead to medication errors. This analysis determined that the name similarity between Lumizyme was unlikely to result in medication errors with any of the eight products for the reasons presented in Appendices D through H.

4 CONCLUSIONS AND RECOMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Lumizyme, is not vulnerable to name confusion that could lead to medication errors nor is it promotional. Thus the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Lumizyme, for this product at this time.

DMEPA considers this a final review; however, if approval of the NDA is delayed beyond 90 days from the date of this review, the Division of Gastroenterology Products (DGP) should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date.

5 REFERENCES

5.1 REVIEWS

OSE Review #2008-1214 Proprietary Name Labeling Review for Lumizyme (Alglucosidase Alfa) for Injection, Oleszczuk, Z; November 14, 2008.

5.2 DATABASES

1. *Micromedex Integrated Index (<http://csi.micromedex.com>)*

Micromedex contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. *Phonetic and Orthographic Computer Analysis (POCA)*

POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion.

3. *Drug Facts and Comparisons, online version, St. Louis, MO (<http://factsandcomparisons.com>)*

Drug Facts and Comparisons is a compendium organized by therapeutic course; it contains monographs on prescription and OTC drugs, with charts comparing similar products.

4. *AMF Decision Support System [DSS]*

DSS is a government database used to track individual submissions and assignments in review divisions.

5. *Division of Medication Errors Prevention and Analysis proprietary name consultation requests*

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

6. *Drugs@FDA (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)*

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and "Chemical Type 6" approvals.

7. *Electronic online version of the FDA Orange Book (<http://www.fda.gov/cder/ob/default.htm>)*

The FDA Orange Book provides a compilation of approved drug products with therapeutic equivalence evaluations.

8. *U.S. Patent and Trademark Office (<http://www.uspto.gov>)*

USPTO provides information regarding patent and trademarks.

9. Clinical Pharmacology Online (www.clinicalpharmacology-ip.com)

Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. It also provides a keyword search engine.

10. Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at (www.thomson-thomson.com)

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

11. Natural Medicines Comprehensive Databases (www.naturaldatabase.com)

Natural Medicines contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

12. Stat!Ref (www.statref.com)

Stat!Ref contains full-text information from approximately 30 texts; it includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolph's Pediatrics, Basic Clinical Pharmacology, and Dictionary of Medical Acronyms Abbreviations.

13. USAN Stems (<http://www.ama-assn.org/ama/pub/category/4782.html>)

USAN Stems List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

Red Book contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

15. Lexi-Comp (www.lexi.com)

Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

16. Medical Abbreviations Book

Medical Abbreviations Book contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, BLA, and ANDA products currently under review by the Center. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.¹

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity and hold a Center for Drug Evaluation and Research (CDER) Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and focuses on the avoidance of medication errors.

FMEA is a systematic tool for evaluating a process and identifying where and how it might fail.² DMEPA uses FMEA to analyze whether the drug names identified with orthographic or phonetic similarity to the proposed proprietary name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. Accordingly, the DMEPA staff considers the product characteristics associated with the proposed drug throughout the risk assessment because the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, DMEPA staff considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.³ DMEPA provides the product characteristics considered for this review in section one.

¹ National Coordinating Council for Medication Error Reporting and Prevention.
<http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

³ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

The Division of Medication Error Prevention and Analysis considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA also compares the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. DMEPA staff also examines the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly and even dissimilarly spelled drug name pairs to appear very similar to one another. The similar appearance of drug names when scripted has led to medication errors. The DMEPA staff applies expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g., "T" may look like "F," lower case 'a' looks like a lower case 'u,' etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details). In addition, the DMEPA staff compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. If provided, DMEPA will consider the Applicant's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Applicant has little control over how the name will be spoken in clinical practice.

Table 1. Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name.

Type of similarity	Considerations when searching the databases		
	Potential causes of drug name similarity	Attributes examined to identify similar drug names	Potential Effects
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	- Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication - Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstrokes Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, the DMEPA staff also considers the potential for the proposed proprietary name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the safety of the proposed proprietary name or product based on professional experience with medication errors.

1. Database and Information Sources

DMEPA staff conducts searches of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name using the criteria outlined in Section 2.1. Section 6 provides a standard description of the databases used in the searches. To complement the process, the DMEPA staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the DMEPA staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel.

2. CDER Expert Panel Discussion

DMEPA conducts an Expert Panel Discussion to gather CDER professional opinions on the safety of the proposed product and the proposed proprietary name. The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the DMEPA staff to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

3. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, conducts a Failure Mode and Effects Analysis, and provides an overall risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.⁴ When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

⁴ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Section one. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

“Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?”

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names possess similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely effect of the drug name confusion, by asking:

“Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?”

The answer to this question is a central component of the Safety Evaluator’s overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Risk Assessment:

- a. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with DDMAC’s findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].
- b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
- c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
- d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.
- e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

• If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Applicant. However, the safety concerns set forth in criteria a through e are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), Joint Commission on Accreditation of Hospitals (JCOAH), and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and a preventable source of medication error that, in many instances, the Agency and/or Applicant can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Applicants have undertaken higher-leverage strategies, such as drug-name changes, in the past but at great financial cost to the Applicant and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Applicants have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval. (See Section 4 for limitations of the process).

Appendix B: Names previously reviewed and determined not to pose a safety risk.

Name	Name
(b) (4)	Cerezyme
	Coenzyme Q10
Sumycin	Pulmozyme
Lumitne	Lanoxin
Lupizyme	Myozyme
Lumigan	

Appendix C: Names Lacking Orthographic and/or Phonetic Similarity.

Name
(b) (4)
Vegizyme
Cortizyme
Lamisil
Luminal

Appendix D: Proprietary or Established Names used only in Foreign Countries

Proprietary Name	Similarity to Lumizyme	Country	Description
Combizyme	Look	United Kingdom	30 Casein Protease units/gram and 880 Penotsanase units/gram from Bacills and Trichoderma
(b) (4)	(b)	(b) (4)	(b) (4)

Appendix E: Drug products that have never been marketed in the US.

Proprietary Name	Similarity to Lumizyme	Status and Date
(b) (4)	(b)	(b) (4)

Appendix F: Single strength products with multiple differentiating product characteristics

Product name with potential for confusion	Similarity to Lumizyme	Strength	Usual Dose (if applicable)	Differentiating Product Characteristics (Lumizyme vs. Product)
Lumizyme (alglucosidase alfa)		Powder for Injection 50 mg/vial	Usual dose: 20 mg/kg intravenously every 2 weeks	
Unizyme [1] (total proteolytic enzyme activity of 120,000 units/g Protease, Peptizyme SP brand Serrapeptase, Papain, Bromelain, Amylase, Lipase, Rutin, and Alma)	Look	1 capsule	Maintenance: 1 to 2 capsules orally 2 times daily. Acute episodes and injury: 3 to 4 capsules orally 3 times daily.	Dosage Form (Powder for injection vs. Capsule) Route (intravenous vs. oral) Dose (20 mg/kg vs. 1 to 4 capsules) Frequency (every 2 weeks vs. once to 3 times daily)
Unizyme [2] (Subtilisin)	Look	1 tablet	Place one tablet in your normal contact lens case with your contact lens for 10 minutes once per week.	Dosage Form (Powder for injection vs. tablet) Route (intravenous vs. for use in your contact lens case) Dose (20 mg/kg vs. 1 tablet) Frequency (every 2 weeks vs. once a week)

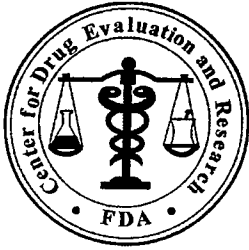
Product name with potential for confusion	Similarity to Lumizyme	Strength	Usual Dose (if applicable)	Differentiating Product Characteristics (Lumizyme vs. Product)
Lumizyme (alglucosidase alfa)		Powder for Injection 50 mg/vial	Usual dose: 20 mg/kg intravenously every 2 weeks	
Ku-zyme (lipase, protease, and amylase)	Look	Capsule: 1,200 units lipase, 15,000 units protease, and 15,000 units amylase	1 or 2 capsules with each meal or snack	Dosage Form (Powder for injection vs. Capsule) Route (intravenous vs. oral) Dose (20 mg/kg vs. 1 to 2 capsules) Frequency (every 2 weeks vs. with each meal or snack)

Appendix G: Products with overlap in strength, dose or achievable dose with multiple differentiating product characteristics

Product name with potential for confusion	Similarity to Lumizyme	Strength	Usual Dose (if applicable)	Differentiating Product Characteristics (Lumizyme vs. Product)
Lumizyme (alglucosidase alfa)		Powder for Injection 50 mg/vial	Usual dose: 20 mg/kg intravenously every 2 weeks	
(b) (4)	(b)	(b) (4)		

Appendix H: Potential confusing name with numerical similarity in strength or dose

Lumizyme (alglucosidase alfa)	Powder for Injection 50 mg/vial	Usual dose: 20 mg/kg intravenously every 2 weeks
Failure Mode: Name confusion	Causes (could be multiple)	Effects
Lincomycin <u>Dosage Form:</u> Injection <u>Strength:</u> 150 mg/mL and 30 mg/mL <u>Dosing Range:</u> <u>Adults:</u> 600 mg IM q24h or 600 mg IV q12h <u>Pediatric:</u> 10 to 20 mg/kg/day depending on the severity of the infection may be infused in divided doses as described above for adults	Orthographic similarity (both names contain the same number of upstrokes, 1 (capital 'L'), the beginning of both names (‘Lin-’ vs. ‘Lum-’ may appear similar when scripted, the letter ‘y’ in each is located in similar positions (7th letter vs. 6th letter), and the 6th letter of Lincomycin (‘z’) and the 5th letter of Lumizyme (m) may look similar when scripted. Possible similar numerical dose (20 units/kg vs. 20 mg/kg) Overlapping route of administration (intravenous infusion.	In addition to orthographic differences, a strict distribution system that is proposed for Lumizyme and the difference in frequency will minimize the likelihood of medication error in the usual practice setting. <i>Rationale:</i> The orthographic differences between the two products will help minimize the likelihood of medication error in the usual practice setting. The length of each name is different (10 letters vs. 8 letters), each name has a different number of down strokes (1, lower case ‘y’ vs. 2, lower case ‘z’ and ‘y’), the middle of each name (‘-co-’ vs. ‘-i-’) appears different when scripted, and the endings of each name (‘-cin’ vs. ‘- me’) appears different when scripted. Lumizyme has a proposed strict distribution plan. The Applicant for this product currently registers all prescribing physicians for the other alglucosidase alfa product marketed in the United States and proposes to maintain this registry for the proposed product as well. The Applicant also registers each patient and sends individualized doses to hospitals for the patient to receive each infusion. A team will be dedicated to review each order to ensure that each patient is receiving the correct drug and dose based on the diagnosis of the patient. All prescription processing and screening takes place at a company run central site. Additionally, all the physicians and sites where infusions are given will be required to complete annual training. Although, Lincomycin and Lumizyme do have overlapping doses; the frequency (once to twice daily vs. once every two weeks) of each product is different. Since the frequency will most likely be included on a prescription the possibility of a medication error is minimized.



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: November 14, 2008

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Director, Division of Gastroenterology Products

Through: Todd Bridges, RPh, Team Leader *Todd Bridges 11/14/08*
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Division of Medication Error Prevention and Analysis

From: Zachary Oleszczuk, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis *Z 11/14/08*

Subject: Proprietary Name and Labeling Review

Drug Name(s): Lumizyme (Alglucosidase Alfa) for Injection 50 mg/vial

Application Type/Number: BLA 125291

Applicant: Genzyme Corporation

OSE RCM #: 2008-1215

*** Note: This review contains proprietary and confidential information that should not be released to the public. ***

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EXECUTIVE SUMMARY

The results of the Proprietary Name Risk Assessment found that the proposed name, Lumizyme, is not vulnerable to name confusion that could lead to medication errors in the United States of America. Thus, the Division of Medication Error Prevention and Analysis has no objection to the use of the proprietary name, Lumizyme, for this product. If any of the proposed product characteristics as stated in this review are altered prior to approval of the product, the Division of Medication Error Prevention and Analysis rescinds this Risk Assessment finding, and recommends that the name be resubmitted for review. Furthermore, this name must be re-evaluated approximately 90 days prior to the expected approval of the BLA. A re-review of the name prior to BLA approval will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

The results of the Label and Labeling Risk Assessment found that the proposed container label and carton labeling are vulnerable to confusion with the container label and carton labeling of the currently marketed product Myozyme because of their similarity in color, layout, and size. The medication error prevention and analysis staff believes the risk we have identified can be addressed prior to approval of the application and provides a recommendation in Section 5.2 that aims at reducing the risk of medication errors.

1 BACKGROUND

1.1 INTRODUCTION

This consult was written in response to a request from the Division of Gastroenterology Products (DGP) to evaluate the product for its potential to contribute to medication errors. The proposed name, Lumizyme, is evaluated to determine if the name could potentially be confused with other proprietary or established drug names. Draft container label, carton and insert labeling were provided for review and comment.

1.2 REGULATORY HISTORY

Lumizyme is the second BLA for the active moiety Alglucosidase Alfa. The first BLA for Alglucosidase Alfa is BLA #125141 and is currently marketed in the United States under the proprietary name Myozyme.

The Myozyme BLA #125141 requested approval of both the 160 liter and 2000 liter production scale for Alglucosidase Alfa, although patients treated in the clinical trials in support of this BLA were treated only with the 160 liter product. During evaluation of the two proposed products, the Agency determined that even though the two products are the same active moiety, the two products are not comparable in Chemistry, Manufacturing and Controls, nonclinical and clinical pharmacology assessments. Therefore, the Applicant Genzyme withdrew the 2000 liter product from BLA #125141 on December 12, 2005. The Agency approved the 160 liter product for BLA #125141 on April 28, 2006.

Genzyme then submitted a supplement (supplement 65) for BLA 125141 in October of 2007. The supplement contained biochemical, nonclinical, and clinical data that was intended to show comparability of the 2000 liter product to the 160 liter product. Following a review of this data, the Agency found that there was insufficient information available to establish the comparability of the 160 liter and 2000 liter products. In particular, there was very limited clinical data available with the 2000 liter product that would have allowed the Agency to make a reasonable assessment of comparability to the 160 liter product. The Agency also had concerns that due to the difference in the manufacturing processes, the 2000 liter product may be less potent than the 160 liter product, although this could not be definitively established given the limitations of the data.

On April 15, 2008, the FDA advised Genzyme to submit a new BLA with clinical data to support a separate licensure of the 2000 liter Alglucosidase Alfa product. BLA 125291 for the 2000 liter Alglucosidase Alfa product was submitted to the Agency on May 30, 2008, and proposed proprietary name is the subject of this review.

1.2.1 Established Name

Although the Agency determined that the 160 liter product and 2000 liter product were not comparable products, the products were both assigned the established name Alglucosidase Alfa by the United States Adopted Names Council (USAN). Although the Agency believes that the products are different and that they should not share the same established name, USAN reiterated that a separate established name is not given based on a manufacturing process and that the use of the established name, Alglucosidase Alfa, is appropriate for both the 160 liter and 200 liter products based on the current process of assigning established names.

1.2.2 Availability of Alglucosidase Alfa Products

The 2000 liter product has already been approved in Canada, Europe and other countries throughout the world. The proposed Alglucosidase Alfa (2000 L) product is currently marketed outside of the United States under the proprietary name Myozyme. Myozyme marketed in the United States is the Alglucosidase Alfa 160 liters product. The 160 liter product is only marketed in the United States. See table 1 for availability of Alglucosidase Alfa products.

Table 1: Availability of Alglucosidase Alfa products

Availability of Alglucosidase Alfa products		
	Proprietary Name Outside of the United States	Proprietary Name in the United States
Alglucosidase Alfa Product (2000 liters)	Myozyme	Proposed Product
Alglucosidase Alfa Product (160 liters)	Not Available Outside of the United States	Myozyme

1.2.3 Proposed Name Change

Genzyme submitted a request to switch the proprietary name, Myozyme, from the currently marketed 160 liter product to the proposed 2000 liter product if the 2000 liter product is approved. This would allow for a global proprietary name for the 2000 liter product. However, the Division of Gastroenterology Products (DGP) along with input from the Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Drug Marketing, Advertising, and Communications (DDMAC) opposed the name change. The Agency informed Genzyme that they would not be granted the proprietary name switch.

Following the communication with the Agency that Genzyme would not be permitted to switch the proprietary name of the Alglucosidase Alfa 160 liter product for the proposed 2000 liter product, Genzyme submitted the name (b) (4) for the 2000 liter product. DDMAC objected to the name (b) (4) and the Division of Gastroenterology Products concurred with DDMAC (OSE Review #2008-1214, dated August 11, 2008). Genzyme then submitted the alternate name "Lumizyme" for review.

1.3 PRODUCT INFORMATION

Lumizyme is indicated for long-term use in patients with late-onset Pompe disease. The recommended dosage is 20 mg/kg administered every 2 weeks as an intravenous infusion. To prepare an infusion, each vial is reconstituted with 10.3 mL of Sterile Water for Injection, USP. Reconstituted Lumizyme (5 mg/mL) should then be diluted in 0.9% Sodium Chloride for Injection, USP to a final concentration of 0.5 mg/mL to 4 mg/mL. Lumizyme should be infused over approximately 4 hours. Lumizyme, which should be stored under refrigeration, will be supplied in 20 mL vials containing 50 mg of lyophilized Alglucosidase Alfa.

2 METHODS AND MATERIALS

This section consists of two sections which describe the methods and materials used by the Division of Medication Error Prevention and Analysis staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment) and label, labeling, and/or packaging risk assessment (see 2.2 Label and Labeling Risk Assessment). The primary focus for both of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.¹

2.1 PROPRIETARY NAME RISK ASSESSMENT

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name, Lumizyme, and the proprietary and established names of drug products existing in the marketplace and those pending IND, BLA, NDA, and ANDA products currently under review by CDER.

¹ National Coordinating Council for Medication Error Reporting and Prevention.
<http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

For the proprietary name, Lumizyme, the Medication Error Staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see section 2.1.1 for detail) and held a CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see section 2.1.3). Additionally, we conducted a search of the Adverse Event Reporting System (AERS) database to search for any additional names that may potentially be confused with the proposed proprietary name (see section 2.2). The Division of Medication Error Prevention and Analysis also conducts internal FDA prescription analysis studies (see 2.1.2), and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (see detail 2.4). The overall risk assessment is based on the findings of a Failure Modes and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors. FMEA is a systematic tool for evaluating a process and identifying where and how it might fail.² FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.³ Our Division uses the clinical expertise of the Medication Error Staff to anticipate the conditions of the clinical setting that the product is likely to be used in based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap, or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. As such, the Staff consider the product characteristics associated with the proposed drug throughout the risk assessment, since the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed drug name include, but are not limited to established name of the proposed product, the proposed indication, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, we consider the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.⁴

² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

³ National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

⁴ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

2.1.1 Search Criteria

The Medication Error Staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted as outlined in Appendix A.

For this review, particular consideration was given to drug names beginning with the letter 'L' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.^{5,6}

To identify drug names that may look similar to Lumizyme, the Staff also consider the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (8 letters), upstrokes (one capital letter 'L'), downstrokes (two, lower case 'z' and 'y'), cross-strokes (none), and dotted letters (one; lower case 'i'). Additionally, several letters in Lumizyme may be vulnerable to ambiguity when scripted, including the letter 'L' may appear as capital 'Z' or 'C'; lower case 'u' may appear as a lower case 'a', 'i', 'n', 'v', 'y', or letter combinations lower case 're'; lower case 'm' may appear as a lower case 'n', 'r', 'z', letter combination 'ss' or 'one'; lower case 'i' may appear as a lower case 'e'; lower case 'z' may appear as a lower case 'm'; lower case 'y' may appear as lower case 'u'; and lower case 'e' appears a lower case 'a', 'l', 'i' or 'p'. As such, the Staff also considers these alternate appearances when identifying drug names that may look similar to Lumizyme.

When searching to identify potential names that may sound similar to Lumizyme, the Medication Error Staff search for names with similar number of syllables in the name (3 syllables), stresses (Lu-mi-zyme, lu-Mi-zyme, lu-mi-Zyme), and placement of vowel and consonant sounds. In addition, several letters in Lumizyme may be subject to interpretation when spoken, including the letter 'u' may be interpreted as 'y' or other vowel; 'm' may be interpreted as 'n' or 'z'; the letter 'z' may be interpreted as 'm' or 'x'; and the letter 'y' may be interpreted as 'u' or other vowel. The Applicant's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

The Staff also consider the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting. For this review, the Medication Error Staff were provided with the following information about the proposed product: the proposed proprietary name (Lumizyme), the established name (alglucosidase alfa), proposed indication (late-onset Pompe disease), strength (50 mg/vial), dose (20 mg/kg), frequency of administration (one every 2 weeks), route (intravenous infusion) and dosage form of the product (lyophilized powder for reconstitution). Appendix A provides a more detailed listing of the product characteristics the Medication Error Staff general take into consideration.

Lastly, the Medication Error Staff also consider the potential for the proposed name to inadvertently function as a source of error for reasons other than name confusion. Postmarketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. As such, these broader safety implications of the name are considered and evaluated throughout this assessment and the Medication Error Staff provide additional comments related to the safety of the proposed name or product based on their professional experience with medication errors.

⁵ Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at <http://www.ismp.org/Tools/confuseddrugnames.pdf>

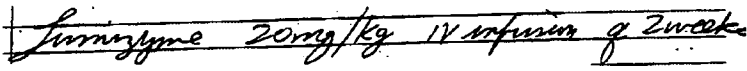
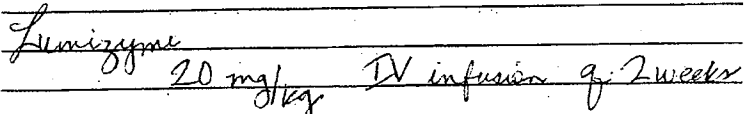
⁶ Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

2.1.2 FDA Prescription Analysis Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Lumizyme with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ a total of 123 healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The results are used by the Safety Evaluator to identify any orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of Lumizyme in handwriting and verbal communication of the name, two inpatient medication orders are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These prescriptions are optically scanned and one prescription is delivered to a random sample of 123 participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants send their interpretations of the orders via e-mail to the medication error staff.

Figure 1. Lumizyme (conducted on September 03, 2008)

MEDICATION ORDER	VERBAL PRESCRIPTION
<u>Inpatient Medication Order #1:</u> 	Lumizyme 20 mg/kg IV q 2 weeks
<u>Inpatient Medication Order #2:</u> 	

2.1.3 Database and Information Sources

The proposed proprietary name, Lumizyme, was provided to DMEPA to conduct a search of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to Lumizyme using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 6. To complement the process, the Medication Error Staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the Medication Error Staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

2.1.4 CDER Expert Panel Discussion

An Expert Panel Discussion is held by the Division of Medication Error Prevention and Analysis to gather CDER professional opinions on the safety of the product and the proprietary name, Lumizyme. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of Medication Error Prevention and Analysis Staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC).

The pooled results of the medication error staff were presented to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

2.1.5 Medication Error Risk Assessment

Since Alglucosidase Alfa is currently marketed in the United States marketplace, the Division of Medication Error Prevention and Analysis conducted a search of the Adverse Event Reporting System (AERS) database to determine if there are any medication errors associated with name confusion or labeling confusion which may be indicative of potential name confusion or labeling confusion with Lumizyme.

The Division of Medication Error Prevention and Analysis searched the FDA Adverse Event Reporting System (AERS) database on September 30, 2008 using the MedRA High Level Group Term (HLGT) "Medication Errors" and Preferred Term (PT) "Pharmaceutical product complaint" as search criteria for Reactions. The search criteria used for Products were active ingredient "alglu%", trade name "Myo%" and verbatim substance names "alglu%", and "myo%".

The cases were manually reviewed to determine if a medication error occurred. Those cases that did not describe a medication error were excluded from further analysis. The cases that described a medication were categorized by type of error. The Safety Evaluator reviewed the cases within each category to identify factors that contributed to the medication errors, and to ascertain if these risks might apply to the proposed Lumizyme product.

2.1.6 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1.1, the Safety Evaluator Risk Assessment applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Modes and Effects Analysis and provide an overall risk of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.⁷ When applying FMEA to assess the risk of a proposed proprietary name, the Division of Medication Error Prevention and Analysis seeks to evaluate the potential for a proposed name to be confused with another drug name as a result of the name confusion and cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to look- or sound-alike drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

⁷ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

In order to perform an FMEA of the proposed name, the Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is not yet marketed, the Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Appendix A. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, expert panel evaluation, and studies, and identifies potential failure modes by asking: "Is the name Lumizyme convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?" An affirmative answer indicates a failure mode and represents a potential for Lumizyme to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names possess similarity that would cause confusion at any point in the medication use system and the name is eliminated from further review.

In the second stage of the Risk Assessment, all potential failure modes are evaluated to determine the likely *effect* of the drug name confusion, by asking "Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?" The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would ultimately not be a source of medication errors in the usual practice setting, the name is eliminated from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend that an alternate proprietary name be used. In rare instances, the FMEA findings may provide other risk-reduction strategies, such as product reformulation to avoid an overlap in strength or an alternate modifier designation may be recommended as a means of reducing the risk of medication errors resulting from drug name confusion.

The Division of Medication Error Prevention and Analysis will object to the use of proposed proprietary name when the one or more of the following conditions are identified in the Safety Evaluator's Risk Assessment:

1. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].
2. The Division of Medication Error Prevention and Analysis identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
4. The proposed proprietary name contains an USAN stem, particularly in a manner that is contradictory to the USAN Council's definition.

5. Medication Error Staff identify a potential source of medication error within the proposed proprietary name. The proprietary name may be misleading, or inadvertently introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

In the event that our Division objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, we will provide a contingency objection based on the date of approval: whichever product is awarded approval first has the right to the use the name, while we will recommend that the second product to reach approval seek an alternative name.

If none of these conditions are met, then we will not object to the use of the proprietary name. If any of these conditions are met, then we will object to the use of the proprietary name. The threshold set for objection to the proposed proprietary name may seem low to the Applicant; however, the safety concerns set forth in criteria 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including the Institute of Medicine, World Health Organization, Joint Commission, and Institute for Safe Medication Practices, which have examined medication errors resulting from look- or sound-alike drug names and called for Regulatory Authorities to address the issue prior to approval.

Furthermore, we contend that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, can be identified and remedied prior to approval to avoid patient harm.

Additionally, postmarketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to remedy post-approval. Educational efforts and so on are low-leverage strategies that have proven to have limited effectiveness at alleviating the medication errors involving drug name confusion. Higher-leverage strategies, such as drug name changes, have been undertaken in the past; but at great financial cost to the Applicant, and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for the approving the error-prone proprietary name. Moreover, even after Applicant's have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioner's vocabulary, and as such, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, we believe that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval (see limitations of the process).

If our Division objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the FMEA process is used to identify strategies to reduce the risk of medication errors. We are likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name, and so we may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

2.2 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container label and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.⁸

Because the Medication Error Prevention and Analysis staff analyzes reported misuse of drugs, the staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. We use FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product, the Applicant submitted the following labels and labeling for our review on July 25, 2008 (See Appendices H and I):

- Container Labels: 50 mg of Lumizyme and Myozyme
- Carton Labeling: 50 mg of Lumizyme and Myozyme
- Insert Labeling (no image)

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

Medication Error Prevention and Analysis staff searches identified 11 names as having some similarity to the name Lumizyme.

Eight of the 11 names were thought to look like Lumizyme; these names include: (b) (4) Cerezyme, (b) (4), Coenzyme Q10, Sumycin, Pulmozyme, Myozyme, and Lumitene. One name, Lanoxin, was thought to sound similar to Lumizyme. Two of the 11 names, Lumigan and Lupizyme, were thought to look and sound similar to Lumizyme.

The proposed proprietary name, Lumizyme, does not contain a USAN stem as of the last date searched, August 28, 2008.

3.1.2 CDER Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by the Medication Error Prevention Staff (see section 3.1.1 above), and did not provide any additional names orthographically or phonetically similar to Lumizyme.

⁸ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

DDMAC had no objection regarding the proposed name from a promotional perspective but did comment that the name Lumizyme could possibly be confused with Lumigan.

3.1.3 FDA Prescription Analysis Studies

A total of twenty-eight (28) practitioners responded, none of the responses overlapped with existing or proposed drug names. Twenty-two (n=22) participants interpreted the name correctly as “Lumizyme”. The remainder of the responses (n=6) misinterpreted the drug name. Three (n=3) of the misinterpretations occurred in the voice prescription study, with ‘-zyme’ in Lumizyme reported as ‘-zide’(n=1) or ‘-zine’ (n=2). Three (n=3) participants from the Inpatient Medication Order group #1 misinterpreted the ‘Lumi-’ as either ‘Lurmi-’ (n=1), ‘Limi-’ (n=1), or ‘Lim-’ (n=1). See Appendix B for complete results.

3.1.4 Adverse Event Reporting

The search conducted on September 30, 2008, yielded 3 cases. One case was a complaint that the proprietary names Myozyme (alglucosidase alfa) and Fabrazyme (agalsidase beta) are similar and may be confused. There was no patient involvement.

The second case involved a patient that received a Myozyme infusion too quickly. The patient required intervention by stopping the infusion and administering diphenhydramine. Patient recovered and had no lasting effects of the incident. Causality was not reported. The package insert for Myozyme and Lumizyme both provide clear instructions for the stepwise infusion rate necessary for these products.

The third case involved a patient receiving Myozyme that was reconstituted but not further diluted. The patient had to be moved to the intensive care unit for life threatening respiratory distress. The patient recovered in ten minutes with no lasting effects. Causality was not reported. The package insert for Myozyme and Lumizyme both provide clear instructions for the reconstitution and dilution necessary for these products.

3.1.5 Safety Evaluator Risk Assessment

Independent searches by the primary safety evaluator did not result in any additional names thought to look or sound similar to Lumizyme and represent a potential source of drug name confusion. As such, a total of 11 names were analyzed to determine if the drug names could be confused with Lumizyme and if the drug name confusion would likely result in a medication error.

All of the identified names were determined to have some orthographic and/or phonetic similarity to Lumizyme, and thus determined to present some risk for confusion. Thus, Failure Modes and Effects Analysis (FMEA) was then applied to determine if the proposed name, Lumizyme, could potentially be confused with any of the 11 names and lead to medication error. This analysis determined that the name similarity between Lumizyme and the identified names was unlikely to result in medication errors for all of the eleven products. See Appendices C through F for our evaluation of the 11 products identified.

3.2 LABEL AND LABELING RISK ASSESSMENT

3.2.1 Container Label

The proposed container label for Lumizyme is almost identical to the container label for Myozyme with the exception of the proprietary name, NDC number and graphic of a person.

3.2.2 Carton Labeling

The proposed carton labeling for Lumizyme is almost identical to the carton labeling for Myozyme with the exception of the proprietary name, NDC number and graphic of a person.

3.2.3 Package Inset Labeling

No comments at this time.

4 DISCUSSION

4.1 PROPRIETARY NAME RISK ASSESSMENT

The results of the Proprietary Name Risk Assessment found that the proposed name, Lumizyme, has some similarity to other proprietary and established drug names, but the findings of the FMEA process indicate that the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors.

The findings of the Proprietary Name Risk Assessment are based upon current understanding of factors that contribute to medication errors involving name confusion. Although we believe the findings of the Risk Assessment to be robust, our findings do have limitations. First, because our assessment involves a limited number of practitioners, it is possible that the analysis did not identify a potentially confusing name. Also, there is some possibility that our Risk Assessment failed to consider a circumstance in which confusion could arise. However, the Division of Medication Error Prevention and Analysis believes that these limitations are sufficiently minimized by the use of an Expert Panel and the FDA Prescription studies, that involved 123 FDA practitioners.

However, our risk assessment also faces limitations beyond the control of the Agency. First, our risk assessment is based on current health care practices and drug product characteristics, future changes to either could increase the vulnerability of the proposed name to confusion. Since these changes cannot be predicted for or accounted by the current Proprietary Name Risk Assessment process, such changes limit our findings. To help counterbalance this impact, the Division of Medication Error Prevention and Analysis recommends that the proprietary name be re-submitted for review if approval of the product is delayed beyond 90 days.

4.2 LABEL AND LABELING RISK ASSESSMENT

Our analysis of the proposed labels and labeling noted a visual similarity to the currently marketed Myozyme. Both products use the same blue and green colors on the labels and labeling. Although the color schemes are reversed, using the same colors on the labels and labeling of both products diminishes the usefulness of color for product differentiation. Although the labels and labeling will have different proprietary names, they will have the same established name and identical product characteristics (strength, dosage form, carton size, and container size).

We acknowledge that these products will be distributed directly to the institutions from the manufacturers and will be labeled with the intended patient's name. However, the container label and carton labeling will be the only way for the healthcare professional to determine if the correct product has been shipped. Thus, the labels and labeling for these 2 products should look significantly different.

5 CONCLUSIONS AND RECOMMENDATIONS

5.1 COMMENTS TO THE DIVISION

The Proprietary Name Risk Assessment findings indicate that the proposed name, Lumizyme, does not appear to be vulnerable to name confusion that could lead to medication errors in the United States of America. As such, the Division of Medication Prevention and Analysis does not object to the use of the proprietary name, Lumizyme, for this product. Additionally, DDMAC has no objections to the proposed name, Lumizyme, from a promotional perspective. If any of the proposed product characteristics as stated in this review are altered prior to approval of the product, the Division of Medication Error Prevention and Analysis rescinds this Risk Assessment finding, and recommends that the name be resubmitted for review. Furthermore, this name must be re-evaluated approximately 90 days prior to the expected approval of the BLA. A re-review of the name prior to BLA approval will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

The Label and Labeling Risk Assessment findings indicate that the similarity of the proposed container labels and carton labeling to the currently marketed product, Myozyme, introduces vulnerability to confusion that could lead to medication errors. DMEPA believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides a recommendation in Section 5.2 that aim at reducing the risk of medication errors.

The Division of Medication Error Prevention would appreciate feedback on the final outcome of this review. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Cheryle Milburn, Project Manager, at 301-796-2084.

5.2 COMMENTS TO THE APPLICANT

5.2.1 *Proprietary Name*

The Division of Medication Error Prevention and Analysis has no objections to the use of the proprietary name, Lumizyme, for this product at this time. If any of the proposed product characteristics as stated in this review are altered prior to approval of the product, the Division of Medication Error Prevention and Analysis rescinds this Risk Assessment finding, and recommends that the name be resubmitted for review. Additionally, this name must be re-evaluated approximately 90 days prior to the expected approval of the BLA.

5.2.2 *Container Label and Carton Labeling*

The Lumizyme label is too similar in appearance to your Myozyme product. Both products share the same established name and have identical product characteristics with exception of the manufacturing process and the proprietary name and use a similar color scheme.

Although the colors are reversed, using the same colors on the labels and labeling of both products diminishes the usefulness of color for product differentiation and may lead to confusion between the two products. Since the label and labeling will be the only way a practitioner can assure the correct product has been shipped, differentiating the label and labeling is especially important for these two products.

Revise the proposed container labels and carton labeling so that the labels and labeling are well differentiated from the currently marketed Myozyme container labels and labeling and do not share a common color scheme.

6 REFERENCES

6.1 DATABASES

1. *Adverse Events Reporting System (AERS)*

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufacturers that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential postmarketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

2. *Micromedex Integrated Index (<http://weblern/>)*

Contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

3. *Phonetic and Orthographic Computer Analysis (POCA)*

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. This is a database which was created for DMEDP, FDA.

4. *Drug Facts and Comparisons, online version, St. Louis, MO (<http://weblern/>)*

Drug Facts and Comparisons is a compendium organized by therapeutic Course; contains monographs on prescription and OTC drugs, with charts comparing similar products.

5. *AMF Decision Support System [DSS]*

DSS is a government database used to track individual submissions and assignments in review divisions.

6. *Division of Medication Error Prevention and Analysis proprietary name consultation requests*

This is a list of proposed and pending names that is generated by our Division from the Access database/tracking system.

7. *Drugs@FDA (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)*

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name and generic drugs and therapeutic biological products; prescription and over-the-counter human drugs and therapeutic biologicals, discontinued drugs and “Chemical Type 6” approvals.

8. *Electronic online version of the FDA Orange Book*
(<http://www.fda.gov/cder/ob/default.htm>)

Provides a compilation of approved drug products with therapeutic equivalence evaluations.

9. *USPTO* (<http://www.uspto.gov>)

Provides information regarding patent and trademarks.

10. *Clinical Pharmacology Online* (<http://weblern/>)

Contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. Provides a keyword search engine.

11. *Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at* www.thomson-thomson.com

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and proprietary names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

12. *Natural Medicines Comprehensive Databases* (<http://weblern/>)

Contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

13. *Stat!Ref* (<http://weblern/>)

Contains full-text information from approximately 30 texts. Includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolph's Pediatrics, Basic Clinical Pharmacology and Dictionary of Medical Acronyms Abbreviations.

14. *USAN Stems* (<http://www.ama-assn.org/ama/pub/category/4782.html>)

List contains all the recognized USAN stems.

15. *Red Book Pharmacy's Fundamental Reference*

Contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

16. *Lexi-Comp* (www.pharmacist.com)

A web-based searchable version of the Drug Information Handbook.

17. *Medical Abbreviations Book*

Contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

The Medication Error Staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. The Division of Medication Error Prevention also compares the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. The Medication Error Staff also examine the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly *and* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has lead to medication errors. The Medication Error Staff apply their expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (i.e. ‘T’ may look like ‘F,’ lower case ‘a’ looks like a lower case ‘u,’ etc), along with other orthographic attributes that determine the overall appearance of the drug name when scripted (see detail in Table 1 below). Additionally, since verbal communication of medication names is common in clinical settings, the Medication Error Staff compare the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, we will consider the Applicant’s intended pronunciation of the proprietary name. However, because the Applicant has little control over how the name will be spoken in practice, we also consider a variety of pronunciations that could occur in the English language.

Table 1. Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name

Type of similarity	Considerations when searching the databases		
	Potential causes of drug name similarity	Attributes examined to identify similar drug names	Potential Effects
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	- Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication - Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstrokes Downstrokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Appendix B: FDA Prescription Study Responses for Lumizyme.

[illegible]

Appendix C: Products that lack orthographic and phonetic similarity to Lumizyme.

Product name with potential for confusion	Similarity to Lumizyme
(b) (4)	(b)
(b) (4)	(b)
Sumycin	Look
Pulmozyme	Look
Lumitene	Look
Lanoxin	Sound
Myozyme	Look

Appendix D: Proprietary name of foreign drug.

Proprietary Name	Similarity to Lumizyme	Strength	Usual Dose	Country
Lupizyme (Pepsin, Amylase, and vitamin b substances)	Look and Sound	Not Available	Not available	India

Appendix E: Product with no numerical overlap in strength and dose.

Product name with potential for confusion	Similarity to Lumizyme	Dosage Form and Strength	Usual Dose (if applicable)	Source
Lumizyme (alglucosidase alfa)		Powder for Injection 50 mg/vial	Usual dose: 20 mg/kg intravenously every 2 weeks	
Lumigan (Bimatoprost)	Look and Sound	Ophthalmic Solution 0.03%	One drop in the affected eye(s) once daily in the evening	Approved package insert

Appendix F: Products with numerical overlap in strength and dose.

Failure Mode: Name confusion	Causes (could be multiple)	Effects
Lumizyme (alglucosidase alfa)	Powder for Injection 50 mg/vial	Usual dose: 20 mg/kg intravenously every 2 weeks
Cerezyme (Imiglucerase) <u>Dosage Form:</u> Lyophilized product for injection <u>Strength:</u> 200 units/vial and 400 units/vial <u>Dosing Range:</u> 2.5 units/kg of body weight intravenously 3 times a week to 60 units/kg intravenously once every 2 weeks <u>Usual Dose:</u> 30 units/kg to 60 units/kg intravenously once every two weeks.	Orthographic similarity (both names contain the same number of letters, 8, both names contain the same number of upstrokes, 1 (capital 'C', vs. capital 'L'), both names contain the same numbers of downstrokes, 2 (the letters 'z' and 'y' located in the same positions, 5th and 6th letters), both names contain the same number of cross strokes (0), both names contain the same ending '-zyme', the beginning of both names ('Ce-' vs. 'Lu-' may appear similar when scripted and the fourth letter of each name ('e' vs. 'i' may appear similar when scripted) Possible similar numerical dose (20 units/kg vs. 20 mg/kg) Overlapping dosage form (lyophilized powder for injection), frequency (every 2 weeks), route of administration (intravenous infusion), and prescribing population.	In addition to a strict distribution system that is proposed for Lumizyme, the difference in units of measurement, usual dose, and the limited number of sites that administer both products will minimize the likelihood of medication error in the usual practice setting. <i>Rationale:</i> The risk for medication error is minimized by a strict distribution process that is proposed for Lumizyme. The Applicant for this product currently registers all prescribing physicians for the other alglucosidase alfa product marketed in the United States and proposes to maintain this registry for the proposed product as well. The Applicant also registers each patient and sends individualized doses to hospitals for the patient to receive each infusion. A team will be dedicated to review each order to ensure that each patient is receiving the correct drug and dose based on the diagnosis of the patient. All prescription processing and screening takes place at a company run central site. Additionally, all the physicians and sites where infusions are given will be required to complete annual training given by the Applicant. Although Cerezyme and Lumizyme can have a numerical overlapping dose (20 units/kg vs. 20 mg/kg), the Medical Director of Cerezyme at Genzyme, through email correspondence, stated that the average dose for Cerezyme is 45 units/kg and most patients receive a dose in the range of 30 units/kg to 60 units/kg which does not overlap with Lumizyme 20 mg/kg. The difference in usual doses will help to minimize errors. Additionally, while the route of administration (intravenous infusion), frequency (once every two weeks), and dosage form (lyophilized powder for injection) are the same for both products the units of measurement of each product is different (Cerezyme: units vs. Lumizyme: mg). Since the units of measurement will most likely be included on a prescription the possibility of a medication error is minimized. Furthermore, there are only 42 sites in the United States that infuse both Cerezyme and Alglucosidase Alfa. Since there are a small number of sites that administer both products this will help minimize the potential for medication error.

Failure Mode: Name confusion	Causes (could be multiple)	Effects
Lumizyme (alglucosidase alfa)	Powder for Injection 50 mg/vial	Usual dose: 20 mg/kg intravenously every 2 weeks
Coenzyme Q10 (Ubiquinone) <u>Dosage From:</u> Oral Capsules <u>Strength:</u> 50 mg, 75 mg, 100 mg, 150 mg <u>Usual Dose:</u> 50 mg to 3000 mg orally 1 to 4 times daily.	Orthographic similarity (the beginning of both names may look similar when scripted ('Coen-' vs. 'Lumi-'), both names contain the same letter string '-zyme' in the same positions (5th letter through 8th letter), both names contain the same number of upstrokes, 1 (capital 'C', vs. capital 'L' if the modifier Q10 is omitted from Coenzyme Q10), both names contain the same numbers of downstrokes, 2 (the letters 'z' and 'y' located in the same positions, 5th and 6th letters), and both names contain the same number of cross strokes (0)) Possible similar doses (i.e. a 2.5 kg patient would receive a 50 mg dose of Lumizyme (20 mg/kg) 50 mg is a possible dose of Coenzyme Q10)	In addition to a strict distribution system that is proposed for Lumizyme, the difference in legend status, frequency and route of administration will minimize the likelihood of medication error in the usual practice setting. <i>Rationale:</i> The risk for medication error is minimized by the legend status of each drug. Coenzyme Q10 is available as an over-the-counter product and Lumizyme is proposed as a prescription product that has a strict distribution plan. The Applicant for this product currently registers all prescribing physicians for the other alglucosidase alfa product marketed in the United States and proposes to maintain this registry for the proposed product as well. The Applicant also registers each patient and sends individualized doses to hospitals for the patient to receive each infusion. A team will be dedicated to review each order to ensure that each patient is receiving the correct drug and dose based on the diagnosis of the patient. All prescription processing and screening takes place at a company run central site. Additionally, all the physicians and sites where infusions are given will be required to complete annual training given by the Applicant. Although Coenzyme Q10 and Lumizyme do have overlapping doses; frequency (one to four times daily vs. once every two weeks) and route of administration (oral vs. intravenous infusion) are different. Since the frequency and route of administration will most likely be included on a prescription the possibility of a medication error is minimized.

Appendix G: Adverse Event Reporting System (AERS) Summary

ISR # FDA Receipt Date	Age	Error	Causality	Outcome	Narrative
5196683 12/29/2006	N/A	Name confusion	Look alike and Sound alike names	No Patient involvement	We recently added Myozyme (alfa aglucosidase) to our formulary. We previously added Fabrazyme (agalsidase beta). In addition to being short stability, high-cost meds, they seem to be potentially problematic from a look-alike, sounds-alike scenario
5383665 07/05/2007	7 months of age	Infusion rate error	None reported	Intervention required	Acute cardiac failure, Worsening respiratory failure, Worsening left ventricular dilation, Blood cultures positive, Anemia, Recurrent hives, Erythematous rash spontaneous report received from a physician regarding a 7-month-old male infantile-onset Pompe patient. [redacted] received the first infusion of Myozyme on 19 April 2007 at a dose of 20 mg/kg every other week. The patient's relevant medical history included hospitalization on 6/17 prior to starting Myozyme for respiratory failure and congestive heart failure secondary to cardiomyopathy. Patient was admitted to the hospital in respiratory distress and hypovolemic/cardiogenic shock (cont.) [continuation:] following fever and diarrhea at home for few days, Patient was emergently intubated and a central venous line was placed for treatment of acute heart failure. Upon admission, patient vomited at the time of intubation and was treated with a course of Unasyn (ampicillin and sulbactam) for aspiration pneumonia. Shortly after admission, bronchoscopy revealed near complete compression of the left mainstem bronchus and chest x-rays (CXR) reveal opacification of the left chest. Hemodynamic parameters improved with inotropic support which was gradually decreased. Continuous positive airway pressure (CPAP) trials were started. Results of patient's skin fibroblast study became available during this hospitalization which was consistent with infantile-onset Pompe disease. Treatment with Myozyme was initiated on 19 April 2007.

ISR # FDA Receipt Date	Age	Error	Causality	Outcome	Narrative
5383665 07/05/2007 (continued)	7 months of age	Infusion rate error	None reported	Intervention required	On 06/05/07 the right femoral central venous line (CVL) was replaced with right subclavian Mediport. A 7-day course of vancomycin was administered for Coagulase negative Staphylococcus which grew in a blood culture. All subsequent cultures were negative. On 06/06/07, initial extubation trial was performed but after 1 hour, patient was in severe respiratory distress with an acute decrease in heart rate and oxygen saturation. Patient was bag-mask ventilated and reintubated. Adjustments were made on the patient's cardiac medications to counteract the effect of the beta blockade from his home propranolol. Patient was administered mild, none 1mcg/kg/min and 0.1mcg/kg, carvedilol was started. Nasojejunal (NJ) feedings were started after patient's cardiac function improved. Patient remained on ventilator until 06/07/07 when patient was successfully extubated to hi-level positive airway pressure (BiPAP). On approximately 06/07/07 during second Myozyme infusion, patient experienced hives. On 06/07/07, chest x-ray (CXR) revealed pulmonary infiltrates suggestive that the patient was still in acute cardiac failure. Dobutamine was added intermittently. On 10 May 2007, patient was weaned to CPAP. After 2 days of CPAP, patient developed hypoxia, tachypnea and was placed back on BiPAP. Later that day with worsening gases, patient was re-intubated. Respiratory cultures were negative. Multiple echocardiograms (ECHO) were done throughout the hospitalization and all showed massive biventricular hypertrophy. The patient's ECHOs were variable and didn't always correlate with the patient's clinical condition. On 06/07/07, ECHO showed worsening left ventricular dilation. On 06/07/07, captopril was added for afterload reduction. On 06/07/07 a tracheostomy was performed and the patient tolerated the procedure. For pain management the fentanyl drip was discontinued and Methadone was started. Chloral hydrate was given as needed. On 06/07/07, patient was scheduled for third Myozyme infusion and received pre-medication 30 minutes prior to the onset of the infusion with Tylenol (acetaminophen) 100 mg via NJ tube and hydrocortisone 8 mg IV 30 minutes. Patient developed a diffuse erythematous rash as the infusion started. Infusion was temporarily interrupted and Benadryl (diphenhydramine hydrochloride) was administered for hives. Infusion staff realized the infusion was running faster than ordered and was not being gradually increased as thought. Infusion was restarted and infusion was completed without incident. On 06/07/07 patient was considered recovered without sequelae from the hives and erythematous rash. On 06/07/07, digoxin was added in order to wean milrinone. Repeat echocardiogram (ECHO) was stable and milrinone was weaned over a period of 1 week. On 06/07/07 patient had first tracheostomy tube change and patient was placed on home vent settings with pCO2 at 50%. After tracheostomy, CXRs were more stable and left lung was expanding more. In addition, patient received Diuril (chlorothiazide) and Aldactone (spironolactone) diuretic therapy and carnitina Supplements. Patient was transfused with packed red blood cells (pRBCs) multiple times to improve oxygen therapy (anemia). On 06/07/07, reticulocytes were low and patient was started on iron supplement and Epogen (epoetin alfa). On 06/07/07, patient was discharged from the hospital to step-down rehabilitation unit. In the (cont.)

ISR # FDA Receipt Date	Age	Error	Causality	Outcome	Narrative
5383665 07/05/2007 (continued)	7 months of age	Infusion rate error	None reported	Intervention required	[continuation:] opinion of the reporter, the events of hives and erythematous rash were nonserious, mild in intensity and probably related to Myozyme. In the opinion of the reporter, the other events were unrelated to Myozyme. Follow-up information was received from Genzyme Clinical Immunology on 25 June 2007. On 31 May 2007, IgG titer was 204,800 and negative for in-vitro inhibition for both enzyme activity and uptake. Correction was noted, patient was transfused with pRBCs multiple times to improve oxygen delivery (anemia). Atelectasis was added to the relevant medical history as it occurred prior to Myozyme infusion. Corrective Treatment: Vancomycin, Intubation, milrinone, carvedilol, BiPAP, CPAP, dobutamine, captopril, tracheostomy, Benadryl, Diuril, Aldactone, camitine, transfusion of pRBCs, Epogen, iron supplement, NJ feedings, fentanyl, methadone, chloral hydrate, digoxin
5851864 06/30/2008	54 weeks of age	Dilution Error	None reported	Intervention required for life threatening respiratory distress	Case Description: Spontaneous report received on 17-JUL-2008 from a physician regarding a 54 weeks old female Glycogen storage disease type II patient, initials N-C. The patient received her first dose of Myozyme on an unspecified date administered via an intravenous route at a dose of 150 mg alternately with 100 mg every 15 days. The patient's relevant medical history is continued in additional info section. remarkable for several episodes of infusion associated reactions (refer Manufacturer Report Numbers, POMP-11217, POMp-11241 and POMp-1 000046) and virosis NOS. On 10-JUL-2008, the date of previous planned Myozyme infusion, the patient presented with virosis NOS. Even so it was decided to administer the infusion, but was discontinued after 8 ml of infusion due to onset of an infusion associated reaction. On 17-JUL-2008 the patient was planned to receive a 150 mg infusion with Myozyme. The patient was orally premedicated with hydrocortisone (Solupred) 1mg/kg and dexchlorpheniramine (Polaramine, dose unspecified) on 15 and 16-JUL-2008. Before the infusion she received hydrocortisone (Solupred) 2 mg/kg and 1 vial of dexchlorpheniramine intravenously. At that moment the patient's clinical status was OK. The patient was planned to receive a 150mg Myozyme infusion in 200 ml, but in fact the total infusion volume was only 36 ml. This resulted in a higher concentration than intended. Due to this medication error, a few seconds after the start of infusion the patient experienced acute respiratory distress syndrome (chest indrawing, cyanosis, and oxygen saturation at 40%) that was severe in intensity and life-threatening and required transfer to intensive care unit. Respiratory rate, heart rate and blood pressure were not provided. Myozyme infusion was interrupted. The patient was correctively treated with bag breathing. She recovered within 10 minutes. Myozyme infusion was not resumed. On 17-JUL-2008 the patient had recovered. The next infusion is planned for 6-8. Re-introduction will be performed in ICU. No concomitant medications were reported. The physician assessed the relationship between acute respiratory distress syndrome and Myozyme as related.

ISR # FDA Receipt Date	Age	Error	Causality	Outcome	Narrative
5851864 06/30/2008 (continued)	54 weeks of age	Dilution Error	None reported	Intervention required for life threatening respiratory distress	Follow-up information received on 06/29/08 in the intensive care unit. Physical examination at admission was normal but patient presented with a slightly elevated temperature of 38 degrees Celsius. Infectious work-up performed at admission consisting of chest X-ray, C-reactive protein, white blood cell count, urine analysis and blood analysis were normal. Patient was premedicated with methylprednisolone sodium succinate (Solumedrol) 2mg/kg, dexchlorpheniramine maleate (Polaramine) 1 mg, paracetamol (Doliprane) and (ibuprofen (Advil). Infusion was started at 2:00 pm and planned to end at 10:00 pm. At 6:00 pm the infusion was uneventful! Physician confirmed on 06/29/08 that infusion has been uneventful! He assessed the fever as related to the underlying disease. Patient was still hospitalized in the intensive care unit in a poor clinical status. Patient presented with severe hypertension (150/120 mmHg) requiring treatment with acebutolol hydrochloride (Sectral) 10 mg/kg/day. Patient also presented with mild respiratory distress requiring oxygen. The physician assessed the clinical status as stable compared to the previous week. He assessed the relationship between the fever, hypertension and respiratory distress as not related to Myozyme but to the underlying disease. Additional information received on 29-JUL-2008 indicated that patient presented on 06/29/08 with acute respiratory insufficiency with a fatal outcome. The physician provided no relationship between the fatal acute respiratory insufficiency and Myozyme. Follow-up information received on 05 August 2008 from the Data Safety Monitoring Board (DSMB). Information pertaining to this case report was reviewed by the DSMB and the formal response was received on 05 August 2008. In the opinion of the DSMB, the event is recorded as causing the life-threatening respiratory distress syndrome, ifc, but the patient's TMs rapid recovery makes this diagnosis unlikely. Nevertheless, the DSMB concur with the treating physician that the reaction was life-threatening and likely related to Myozyme. This reaction, while severe, is not unusual, and is probably related to the error in preparing the medication. As in similar cases that the DSMB has reviewed in the past, the DSMB recommended that the clinicians for the patient determine whether the potential for benefit from the medication outweighs the risks associated with these types of reactions.