

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205494Orig1s000**

**CHEMISTRY REVIEW(S)**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

**METHODS VALIDATION REPORT SUMMARY**

**TO:** Yichun Sun, CMC Reviewer

Office of New Drug Quality Assessment (ONDQA)  
E-mail Address: yichun.sun@fda.hhs.gov  
Phone: (301)-796-1388  
Fax: (301)-796-9877

**FROM:** FDA

Division of Pharmaceutical Analysis  
Michael Trehy, MVP Coordinator  
645 S Newstead Avenue  
St. Louis, MO 63110  
Phone: (314) 539-3815

**Through:** John Kauffman, Deputy Director  
Phone: (314) 539-2168

**SUBJECT:** Methods Validation Report Summary

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Application Number: 205494

Name of Product: Cerdelga (eliglustat) Capsules 84 mg

Applicant: Genzyme Corporation

Applicant's Contact Person: Sherwin Sattarzadeh

Address: 500 Kendall Street, Cambridge, MA 02142

Telephone: (908) 450-5300 Fax: (908) 450-5351

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Date Methods Validation Consult Request Form Received by DPA: 13-Nov-2013

Date Methods Validation Package Received by DPA: 13-Nov-2013

Date Samples Received by DPA: 10-Dec-2013

Date Analytical Completed by DPA: 8-Aug-2014

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Laboratory Classification: 1. Methods are acceptable for control and regulatory purposes.   
2. Methods are acceptable with modifications (as stated in accompanying report).   
3. Methods are unacceptable for regulatory purposes.

Comments: See attached memo for analyst's comments and summary of results.



Date: August 8, 2014

To: Yichun Sun, Ph. D., CMC Reviewer, ONDQA  
Marie Kowblansky, Ph. D., CMC Lead, ONDQA

From: Anjanette Smith, Chemist, Division of Pharmaceutical Analysis

Through: John Kauffman, Ph. D., Deputy Director, Division of Pharmaceutical Analysis

Subject: Method Validation for NDA 205494  
Cerdelga® (eliglustat) Capsule, 84mg  
Genzyme Corporation

The following method was evaluated and is acceptable for quality control and regulatory purposes:

- HPLC Purity/Assay, drug substance (BR-05-089-04)

The following methods were evaluated and are acceptable for quality control and regulatory purposes with the following comments:

HPLC chiral purity (BR-05-089-04)

1. The equation for calculating chiral purity should be added.
2. DPA observed that detection and quantification were improved using a wavelength of (b) (4) nm. Solvent absorbance at (b) (4) nm results in a noisy baseline. DPA recommends use of (b) (4) nm or (b) (4) nm instead of (b) (4) nm. When using (b) (4) nm instead of (b) (4) nm, the relative response factor for the peak observed at approximately 14 minutes increases. Please refer to Figure 1 in attachment A.

Gradient HPLC method for ID, Assay, Purity and Content, drug product (QC 360 07)

Drug substance impurities (e.g., (b) (4)) were observed in this test method. DPA suggests that drug substance impurity retention times should be noted in the method to remove them from consideration during calculation of unspecified degradation products.

1. Analyst's work sheets and chromatograms are available at <http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f880770e10>

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/s/  
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MICHAEL L TREHY  
08/18/2014

JOHN F KAUFFMAN  
08/18/2014

**Memorandum**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**Date: August 5, 2014**

**From: Yichun Sun, Ph.D.**  
**Review Chemist, ONDQA**  
**Division of New Drug Quality Assessment II**  
**ONDQA**

**Through: Moo-Jhong Rhee, Ph.D.**  
**Chief, Branch IV**  
**Division of New Drug Quality Assessment II**  
**ONDQA**

**To: CMC Review #1 of NDA 205494**

**Subject: Final Approval Recommendation for NDA 205494**

At the time when the CMC review #1 was written, resolution of issues on **Specifications** of drug substance and drug product, and **Labels and Labeling** was pending. Additionally, the Office of Compliance had not issued an overall “Acceptable” recommendation for the facilities involved in this application.

**Drug Substance Specification**

Since (b) (4) is used in the synthesis of the drug substance, the applicant was requested to include (b) (4) testing in the drug substance specification in the IR letter dated May 6, 2014. Thus, the drug substance specification was not adequate due to lack of testing the residual (b) (4)

The applicant provided the (b) (4) analysis data in the amendment (0035) dated July 15, 2014. The test method used was based on the USP <233> and <730>. The validation parameters meet the ICH Q2 guidelines. The method LOQ was determined to be (b) (4) ppm. Following the method validation, ten recent batches of eliglustat tartrate drug substance were tested; the results show that (b) (4) has not been detected in any of the batch. See table below:

**Levels of (b) (4) in Drug Substance**

DS Batch	Amount of (b) (4)
(b) (4)	

**Evaluation:** The data show that the during the (b) (4) within an insignificant level. Based on the data provided and inherent low toxicity of (b) (4) for the oral drug products, routine testing for (b) (4) in the elemental analysis is deemed not necessary. The response is **satisfactory**.

**Drug Product Specification**

The applicant was requested to update the drug product specification to reflect the change of removing microbial limit testing in the amendment dated December 20, 2013 in the IR letter dated May 6, 2014.

The applicant provided an amendment dated May 9, 2014. The drug product specification has been updated reflecting the change of removing microbial limit testing in the amendment dated December 20, 2013. The updated drug product specification is presented in the following Table.

### Updated Eliglustat Capsule Specification

Test	Method	Acceptance Criteria (Release)	Acceptance Criteria (End of Shelf-Life)
Appearance (Contents)	Visual	White to off-white powder	White to off-white powder
Appearance (Capsule)	Visual	Pearl blue-green opaque cap and pearl white opaque body with 'GZ02' printed in black on the capsule	Pearl blue-green opaque cap and pearl white opaque body with 'GZ02' printed in black on the capsule
Identity	HPLC	The retention time of the principal peak in the sample chromatogram corresponds to the retention time of the principal peak in the reference chromatogram	NA <sup>a</sup>
	UV	Sample spectrum conforms to reference spectrum	NA <sup>a</sup>
Assay	HPLC	(b) (4) to (b) (4) % wt/wt	(b) (4) to (b) (4) % wt/wt
Degradation Products <sup>b</sup>	HPLC	<i>Specified identified degradation products</i>	<i>Specified identified degradation products</i>
		(b) (4) wt/wt	(b) (4) wt/wt
		(b) (4) wt/wt	(b) (4) wt/wt
		<i>Unspecified degradation products</i>	<i>Unspecified degradation products</i>
		No individual > (b) (4) %, wt/wt	No individual > (b) (4) %, wt/wt
		≤ (b) (4) % Total Degradation Products, wt/wt	≤ (b) (4) % Total Degradation Products, wt/wt
Uniformity of Dosage Units	USP <905> Ph. Eur. 2.9.40	Complies	NA <sup>a</sup>
Dissolution	USP <711> Ph. Eur. 2.9.3	Q = (b) (4) % in 30 minutes	Q = (b) (4) % in 30 minutes (b) (4)

**Evaluation:** The drug product specification has been updated reflecting the change of removing microbial limit testing in the amendment dated December 20, 2013. The response is **satisfactory**.

#### **Label/Labeling**

On July 23, 2014, the NDA applicant submitted an amendment providing the finalized mock up carton and blister labels. Additionally, the applicant also agreed to all the CMC changes made to the package insert. All the labels/labeling issues are now **satisfactorily resolved**. The CMC sections of the final package insert, and mock up container labels are attached (**Attachment - 1**).

**Establishment Evaluation**

On July 8, 2014, the office of compliance provided an **Overall Acceptable** recommendation for the facilities involved in the manufacture and test of the drug substance and drug product. The Establishment Evaluation is attached (**Attachment - 2**).

**Recommendation:**

All pending issues on CMC and Label/Labeling are now satisfactorily resolved for the NDA, and the office of compliance provided an **Overall Acceptable** recommendation for the facilities involved in the manufacture and test of the drug substance and drug product. Therefore, from the ONDQA's perspective, this NDA is recommended for **APPROVAL**. An expiration dating period of **24 months** is granted for the drug product of NDA 205494.

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/s/  
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YICHUN SUN  
08/05/2014

MOO JHONG RHEE  
08/05/2014  
Chief, Branch IV

# **NDA 205494**

## **Cerdelga<sup>TM</sup> (eliglustat) Capsules**

### **Genzyme Corporation**

**Yichun Sun Ph.D.  
Tarun Mehta, M.S.  
Hamid Shafiei, Ph.D.**

**Branch IV, Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment**

**CMC REVIEW OF NDA 205494  
For The Division of Gastroenterology and Inborn Errors Products  
(HFD-180)**

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# Chemistry Review Data Sheet

1. NDA: #205494
2. REVIEW #: 1
3. REVIEW DATE: 20-May-2014
4. REVIEWER: Yichun Sun, Ph.D.  
For Drug Substance: Mehta Tarun, M.S.  
For Manufacturing Process: Hamid Shafiei, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 67589	02-January-2004
EOP 2 meeting Memorandum (IND 67589)	26-May-2010

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	20-September-2013
Amendment	25-October-2013
Amendment	9-December-2013
Amendment	7-February-2014
Amendment	14-March-2014
Amendment	9-May-2014

7. NAME & ADDRESS OF APPLICANT:

Name: Genzyme Corporation  
Address: 500 Kendall Street  
Cambridge, MA 02142  
Representative: Sherwin Sattarzadeh  
Telephone: 617-768-6419

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Cerdelga™  
b) Non-Proprietary Name (USAN): Eliglustat Tartrate  
c) Code Name/# (ONDQA only): N/A  
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 1
  - Submission Priority: Priority Review

## 9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: Eliglustat is an inhibitor of glucosylceramide synthase, and acts as a substrate reduction therapy for Gaucher disease type 1 (GD1).

11. DOSAGE FORM: Immediate Release Capsules (hard gelatin capsules)

12. STRENGTH/POTENCY: Each capsule contains 84 mg of eliglustat, which is equivalent to 100 mg of eliglustat tartrate.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

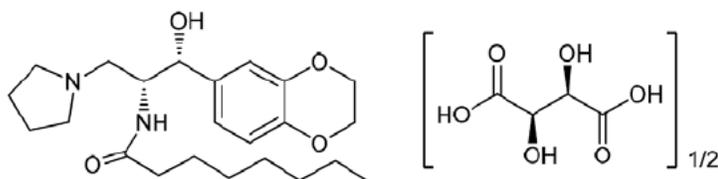
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Octanamide, N-[(1R,2R)-2-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-hydroxy-1-(1-pyrrolidinylmethyl)ethyl]-, (2R,3R)-2,3-dihydroxybutanedioate (2:1)



**Structural Formula of Eliglustat Tartrate**

Empirical formula:  $C_{23}H_{36}N_2O_4 + \frac{1}{2} (C_4H_6O_6)$

Molecular weight: 479.59

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: NA

B. Other Documents: NA

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	----	----
EES	Pending	----	----
Pharm/Tox	N/A	----	----
Biopharm	Acceptable	19-May-2014	T. Chen
LNC	N/A	----	----
Methods Validation	Pending	----	----
DMETS	N/A	----	----
EA	Categorical Exclusion Acceptable	See Review Date Above	Y. Sun
Microbiology	Acceptable	02-January-2014	R. J. Mello

# The Chemistry Review for NDA 205494

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The applicant of this NDA has *not* provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance.

The Office of Compliance has *not* issued an overall “Acceptable” recommendation for the facilities involved in this application.

The label and labeling issues have *not* been resolved.

Therefore, from the ONDQA perspective, this NDA is *not* ready for approval in its present form per 21 CFR 314.125(b)(1)(6), and (13) until these issues are satisfactorily resolved.

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

N/A

### II. Summary of Chemistry Assessments

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

##### Drug Substance

The drug substance Eliglustat tartrate is the (b) (4) Genz-99067. The drug substance’s code name is Genz-112638 which is a (b) (4) salt form of Genz-99067 base.

The DS is (b) (4) off white (b) (4) powder; highly water soluble and moderately soluble in physiological pH buffers. It is classified as BCS Class 1 compound having a (b) (4) molecule with two chiral centers. The DS is a mixture of 1R, 2R stereoisomer with chiral purity of > (b) (4)%. Due to its high solubility, the DS particle size is not considered as an important attribute. Eliglustat tartrate is not photosensitive, stable under short-term exposure to temperature and humidity, , and acidic and basic conditions between the pH 4 to pH 7.

This synthetic process uses (b) (4)

(b) (4)

The drug substance identity, potency and purity were adequately controlled by the drug substance's release specification. Identity was confirmed with two separate spectroscopic analyses, potency was quantitated using reverse phase high pressure liquid chromatographic analysis (RP-HPLC). The purity confirmation was achieved by testing the drug substance for various types of impurities such as chiral impurities (Chiral-HPLC), degradation impurities and starting material presence (RP-HPLC), residual impurities (USP <621>) of solvents and elemental impurities (ICP-MS USP <233>) arise from the catalyst. All the instrumental analytical methods were adequately validated.

During the review it was noted that the applicant was

(b) (4)

Also noted was a potential presence of residual (b) (4), which was used as (b) (4)

The sponsor has agreed to provide the revised specification with an acceptance criterion for (b) (4)

Based on long term stability data through 60 months for one batch stored at  $25 \pm 2^\circ\text{C}/60 \pm 5\% \text{RH}$  and through 48 months for four registration stability batches stored at  $25 \pm 2^\circ\text{C}/60 \pm 5\% \text{RH}$  and  $30 \pm 2^\circ\text{C}/75 \pm 5\% \text{RH}$ , a retest period of (b) (4) months is approved for eliglustat tartrate when stored in the commercial packaging configuration under the long term storage condition.

### Drug Product

The drug product, Cerdelga™ (Eliglustat Tartrate) Capsules, is immediate-release hard gelatin capsules with a pearl blue-green opaque cap and pearl white opaque body, and "GZ02" printed in black on the capsule body. Each size 2 hard gelatin capsule contains 84 mg eliglustat free base (equivalent to 100 mg of eliglustat tartrate) and microcrystalline cellulose, lactose monohydrate, hypromellose and glyceryl behenate/ (b) (4)

The capsules are prepared by (b) (4)

The in-process controls implemented during the manufacture process are: (b) (4)

Eliglustat hard gelatin capsules are packaged in blister cards. Each blister card, which is put inside of a cardboard wallet, contains 14 capsules. Four packs of blister cards are packaged in (56 capsules total) a carton. The drug product specification is adequate to ensure the identity, purity, strength and quality of the drug product. An expiration dating period of (b) (4) months is granted, when stored at the recommended controlled room temperature (b) (4) with excursions permitted from  $15\text{-}30^\circ\text{C}$ ). A

categorical exclusion from the preparation of an environmental assessment is recommended for eliglustat pursuant to 21 CFR Part 25, Subpart C, Categorical Exclusions, Section 25.31 (b), Human drugs and biologics.

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

The Eliglustat tartrate capsules are indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1). The 84 mg capsule should be taken orally twice daily, with or without food.

## C. Basis for Approvability or Not-Approval Recommendation

21 CFR 314.125(b)(1)

- The drug substance specification needs to be revised with proposed limit to control the residual (b) (4)

21 CFR 314.125(b)(13)

- The Office of compliance has not issued an overall "Acceptable" recommendation for the facilities involved in this application.

21CFR 314.125(b)(6)

- Label and labeling issues have not been resolved.

(see the **List of Deficiencies** on p. 126)

## III. Administrative

### A. Reviewer's Signature

/s/ Y. Sun, Ph.D.

### B. Endorsement Block

Tarun Mehta, M.S.  
Reviewer

\_\_\_\_\_  
Date

Hamid Shafiei, Ph.D.  
Reviewer

\_\_\_\_\_  
Date

Yichun Sun, Ph.D.  
Reviewer

\_\_\_\_\_  
Date

Marie Kowblansky, Ph.D.  
Pharmaceutical Assessment lead

\_\_\_\_\_  
Date

Moo-Jhong Rhee, Ph.D.  
Branch Chief

\_\_\_\_\_  
Date



# CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

Catherine Tran-Zwanetz, M.S.  
Project Manager

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Date

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/s/  
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YICHUN SUN  
05/21/2014

TARUN D MEHTA  
05/21/2014

HAMID R SHAFIEI  
05/21/2014

MOO JHONG RHEE  
05/21/2014  
Chief, Branch IV

# Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre- Marketing Applications (Original)

- I. Review Cover Sheet
- II. Application Detail
- III. Filing Checklist
- IV. Manufacturing Summary
- V. Overall Conclusions and Recommendations

## I. Review Cover Sheet

- 1. DMPQ Reviewer: Christina Capacci-Daniel
- 2. NDA/BLA Number: NDA 205494  
Submission Date: Sept 20, 2013  
21<sup>st</sup> C. Review Goal Date:  
PDUFA Goal Date: March 20, 2014

### 3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Cerdelga
Established or Non-Proprietary Name (USAN) and strength:	Eliglustat Tartrate
Dosage Form:	Hard gelatin capsules

### 4. SUBMISSION PROPERTIES:

Review Priority :	PRIORITY
Applicant Name:	Genzyme Corporation
Responsible Organization (OND Division):	DGIEP

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

## II. Application Detail

1. INDICATION: Long-term treatment of adult patients with Gaucher Disease type 1.
2. ROUTE OF ADMINISTRATION: Oral
3. STRENGTH/POTENCY: 84mg (or 100mg of salt)
4. Rx/OTC DISPENSED:   Rx       OTC
5. ELECTRONIC SUBMISSION (yes/no)? YES
6. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V	<input checked="" type="checkbox"/>			NME reviewed under the Program
2.	Breakthrough Therapy Designation		<input checked="" type="checkbox"/>		
3.	Orphan Drug Designation	<input checked="" type="checkbox"/>			
4.	Unapproved New Drug		<input checked="" type="checkbox"/>		
5.	Medically Necessary Determination		<input checked="" type="checkbox"/>		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		<input checked="" type="checkbox"/>		
7.	Rolling Submission		<input checked="" type="checkbox"/>		
8.	Drug/device combination product with consult		<input checked="" type="checkbox"/>		
9.	Complex manufacturing				
10.	Other (e.g., expedited for an unlisted reason)		<input checked="" type="checkbox"/>		

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

### III. FILING CHECKLIST

The following parameters are necessary in order to initiate a full review (i.e., the application is complete enough to start review but may have deficiencies). On **initial** review of the NDA application:

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	Yes	No	Comment
11.	Is all site information complete (e.g., contact information, responsibilities, address)?	<input checked="" type="checkbox"/>		
12.	Do all sites indicate they are ready to be inspected (on 356h)?	<input checked="" type="checkbox"/>		
13.	Is a single comprehensive list of all involved facilities available in one location in the application?	<input checked="" type="checkbox"/>		
14.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	<input checked="" type="checkbox"/>		
15.	Additional notes (non-filing issue)	<input checked="" type="checkbox"/>		
	1. Are all sites registered or have FEI #?	<input checked="" type="checkbox"/>		OMPQ plan to write KTMs for the CHG and CSN sites.
	2. Do comments in EES indicate a request to participate on inspection(s)?	<input checked="" type="checkbox"/>		
	3. Is this first application by the applicant?		<input checked="" type="checkbox"/>	

\*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQuestions. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

<b>B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
16.	Have any Comparability Protocols been requested?		<input checked="" type="checkbox"/>	

<b>IMA CONCLUSION</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
17.	Does this application fit one of the EES Product Specific Categories?	<input checked="" type="checkbox"/>		<ul style="list-style-type: none"> <li>• NME</li> <li>• New Dosage form (CHG) for Genzyme Ltd., Waterford, Ireland</li> </ul>
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?	<input checked="" type="checkbox"/>		
19.	<b>From a CGMP/facilities perspective, is the application fileable?</b> If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	<input checked="" type="checkbox"/>		

## IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements?			
Nanotechnology <input type="checkbox"/>	RTRT Proposal <input type="checkbox"/>	PAT <input type="checkbox"/>	Drug/Device Combo <input type="checkbox"/>
PET <input type="checkbox"/>	Design Space <input type="checkbox"/>	Continuous Mfg <input type="checkbox"/>	Naturally derived API <input type="checkbox"/>
Other (explain):			

Manufacturing Highlights				
<b>1. Drug Substance</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		<input checked="" type="checkbox"/>	(b) (4)

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

(b) (4)



**2. Drug Product**

	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		<input checked="" type="checkbox"/>	 (b) (4)

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

(b) (4)

**3. Facility-Related Risks (e.g., expected in-process testing not being performed, questionable development, unexplained stability failures, data integrity issues, etc.). Describe any potential 21CFR 211 compliance issues.**

- No outstanding facility-related risks that could impact the manufacturing of this product. The drug substance manufacturing facility was last found to be VAI. The two testing facilities were last found to be NAI.

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

**4. Drug Product Facility Inspectional History that could impact the manufacturing of this product.**

- No outstanding Drug Product Facility Inspectional History issues that could impact the manufacturing of this product. Primarily a sterile manufacturer, the drug product site was last found to be VAI.

**Additional information not covered above**

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

**Manufacturing Facilities Chart** (generated from 602A DARRTS report and OMPQ macro):

Establishment Name	FEI Num	District Short	Country Code	Responsibilities	Profile Code	Inspection History, Dates, Classifications	Most Recent Milestone	Comment
GENZYME LTD.	3003809840	WEU	IRL	DP Manufacture, in-process testing, packaging, release testing, stability testing & QA release of DP	CHG	09/30/2011 VAI for sterile DPs	ASSIGNED INSPECTION TO IB (PS&GMP)	CHG profile is new to firm
(b) (4)				DS manufacture, in-process testing, stability testing & release of DS	CSN	12/22/2011 VAI for CSN	ASSIGNED INSPECTION TO IB (PS&GMP)	
				In process testing (b) (4)	CTL	12/04/2009 NAI for CTL	ASSIGNED INSPECTION TO IB (PS&GMP)	
				Release testing (Element analysis)	CTL	04/08/2011 NAI for CTL	OC REC	

## V. Overall Conclusions and Recommendations

<b>Is the application fileable? (yes/no, Yes to questions 11-12) YES</b>
<b>Based on Section IV, is a KTM warranted for any PAI? (yes/no). If yes, please identify the sites in the above chart. YES</b>
<ul style="list-style-type: none"><li>• <b>CHG</b> – The Genzyme, Waterford Ireland site has some (b) (4) (b) (4)</li><li>• <b>CSN</b> – A PAI is recommended for (b) (4)</li></ul>
<b>Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? (yes/no) NO</b>
Comments for 74 Day Letter
1.
2.
3.

## REVIEW AND APPROVAL (DARRTS)

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/s/  
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CHRISTINA A CAPACCI-DANIEL  
11/15/2013

TARA R GOOEN  
11/15/2013

# IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **NDA 205494**

2. DATES AND GOALS:

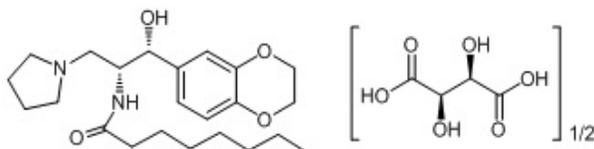
Letter Date: 9/20/2013	Submission Received Date : 9/20/2013
PDUFA Goal Date: 3/20/2014	Filing Date: <b>11/19/2013</b>

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	<b>Cerdelga</b>
Established or Non-Proprietary Name (USAN):	<b>eliglustat tartrate (USAN)</b>
Dosage Form:	<b>Hard capsules</b>
Route of Administration	<b>oral</b>
Strength/Potency	<b>84 mg</b>
Rx/OTC Dispensed:	<b>Rx</b>

4. INDICATION: **Gaucher Disease type 1**

5. DRUG SUBSTANCE STRUCTURAL FORMULA:



6. NAME OF APPLICANT (as indicated on Form 356h): **Genzyme Corporation**

7. SUBMISSION PROPERTIES:

Review Priority:	<b>Expedited Review</b>
Submission Classification (Chemical Classification Code):	<b>Type 1</b>
Application Type:	<b>505(b)(1)</b>
Breakthrough Therapy	<b>No</b>
Responsible Organization (Clinical Division):	<b>Division of Gastrointestinal and Inborn Error Products</b>

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		x	
Clinical Pharmacology			NA (part of review team)
Establishment Evaluation Request (EER)	x		10/11/2013

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Pharmacology/Toxicology			NA (part of review team)
Methods Validation	x		
Environmental Assessment	x		Categorical exclusion
CDRH		x	
Other		x	

## Overall Filing Conclusions and Recommendations

### CMC:

Is the Product Quality Section of the application fileable from a CMC perspective?

Yes  No

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter?

Yes No

### Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective?

Yes  No

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter?

Yes No

### Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective?

Yes  No

Microbiology Filing Issues:

See Microbiology Filing Review for details and for any potential Microbiology review issues.

## Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
no	no	no	no

Is a team review recommended?		Yes
Reviewers already assigned:	NDA: Yichun Sun, PhD Drug substance: Tarun Mehta Drug product manufacture: Hamid Shafiei, PhD Micro: Robert Mello, PhD Biopharmaceutics: Tien-Mien Chen, PhD	

Summary of Critical Issues and Complexities
<p>To ensure that there is sufficient linkage between the proposed commercial formulation and the formulations used in the clinical trials, the applicant was asked to clarify the following statement in the submission, prior to the filing date:</p> <p><i>Formulation descriptors refer to the formulations used in the initiation of each trial and not necessarily to the formulation used throughout the clinical phase or to the clinical phase itself.</i></p> <p>In response to our request, the applicant submitted a tabulation of all formulations that were used during the clinical trials. This information will be evaluated during the course of the full review.</p>

## Initial Quality Assessment

Cerdelga™ (eliglustat) Capsules is intended for long-term treatment of adult patients with Gaucher disease type 1. This product, which has Orphan Drug designation, was developed under IND 67,589. It is formulated as an immediate release hard gelatin capsule for twice daily administration. Each capsule contains 84 mg eliglustat free base (equivalent to 100 mg of eliglustat tartrate) and microcrystalline cellulose, lactose monohydrate, hypromellose and glyceryl behenate (b) (4). The product strength is expressed in conformance with the USP naming policy, i.e. based on the active moiety. The capsules are marketed in blister packages (14 capsules per card and 4 cards per box).

Because eliglustat is a new molecular entity, according to the Chemical Classification Code this is a Type 1 application.

Twenty four months of long term stability data and six months of accelerated data have been submitted with a request for a (b) (4) month expiration dating period.

## FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	√		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	√		
3.	Are all the pages in the CMC section legible?	√		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		

B. FACILITIES*				
* <b>If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential</i> filing issue or a <i>potential</i> review issue.</b>				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	√		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>			NA Synthetic drug substance

	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	√		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	√		

	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	√		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	√		

<b>C. ENVIRONMENTAL ASSESMENT</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	Has an environmental assessment or claim of categorical exclusion been provided?	√		categorical exclusion claimed

<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?	√		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	√		
14.	Does the section contain information regarding the characterization of the DS?	√		
15.	Does the section contain controls for the DS?	√		
16.	Has stability data and analysis been provided for the drug substance?	√		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		√	Not required
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		√	Not required

<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	√		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	√		
21.	Is there a batch production record and a proposed master batch record?	√		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	√		
23.	Have any biowaivers been requested?		√	None required
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	√		
25.	Does the section contain controls of the final drug product?	√		
26.	Has stability data and analysis been provided to support the requested expiration date?	√		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		√	Not required
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		√	Not required

<b>F. METHODS VALIDATION (MV)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
29.	Is there a methods validation package?	√		

<b>G. MICROBIOLOGY</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product	√		The microbiology reviewer has judged the submitted information sufficient

<b>H. MASTER FILES (DMF/MAF)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?		√	There are no references to DMFs; required information regarding the drug substance, excipients, and packaging materials is included directly in the NDA

<b>I. LABELING</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
32.	Has the draft package insert been provided?	√		
33.	Have the immediate container and carton labels been provided?	√		

<b>J. BIOPHARMACEUTICS</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
34.	Does the application contain dissolution data?	X		The proposed dissolution method: USP Apparatus 2 (Paddle) with 75 rpm in 0.1 N HCl 900 mL medium at 37°C
35.	Is the dissolution test part of the DP specifications?	X		The proposed dissolution acceptance criterion: Q <sup>(b)</sup> <sub>(4)</sub> % at 30 min
36.	Does the application contain the dissolution method development report?	X		
37.	Is there a validation package for the analytical method and dissolution methodology?	X		
38.	Does the application include a biowaiver request?		X	Only one strength proposed
39.	Does the application include a IVIVC model?		X	
40.	Is information such as BCS classification mentioned, and supportive data provided?	X		Already determined by FDA as a BCS1 drug.
41.				

42.	Is there any <i>in vivo</i> BA or BE information in the submission?	X		
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*See appended electronic signature page*

*Marie Kowblansky, PhD*

CMC-Lead

Division II

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*{See appended electronic signature page}*

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/s/  
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