

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125359Orig1s000**

**MICROBIOLOGY REVIEW(S)**



Food and Drug Administration  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue,  
Building 51,  
Silver Spring, MD 20993

**Date:** October 14, 2011  
**To:** Administrative File, STN 125359/0  
**From:** Kalavati Suvarna, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB  
**Endorsement:** Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB  
**Subject:** Review memo addendum: Responses to CMC Microbiology Information request dated July 11, 2001 to the BLA. Amendments 0016 (dated 8/18/2011), 0017 (dated 8/30/2011), 0019 (dated 9/30/2011) and 0020 (dated 10/12/2011).  
**US License:** # 1829  
**Applicant:** EUSA Pharma (USA) Inc.  
**Mfg Facility:** **Drug Substance and Drug Product** (b) (4)  
**Product:** Erwinaze™ (Erwinia L-asparaginase for Injection)  
**Dosage:** Sterile lyophilized powder for injection following reconstitution with 0.9% Sodium Chloride Injection USP, supplied in a 3 mL glass vial (10,000 IU/vial)  
**Indication:** Treatment of acute lymphoblastic leukemia as a substitute for E. coli asparaginase  
**Due Date:** August 2, 2011

**Recommendation for Approvability:** The amendments (eCTD sequence numbers 0016, 0017, 0019 and 0020) to BLA 125359/0 were reviewed from a CMC microbiology, sterility assurance, and product quality perspective. The BLA, as amended, is recommended for approval from a microbiology product quality and sterility assurance perspective with the following post-marketing commitments (PMCs):

PMC#1: To conduct a container closure integrity study and determine the sensitivity of the test methods. Submit the final study report with validation data for the container closure integrity tests by December 31, 2011.

PMC#2: To conduct performance qualification of the Erwinaze lyophilization process and submit the qualification data by March 31, 2012.

PMC#3: To provide validation data from the executed protocol for shipping Erwinaze drug product from the (b) (4) to the US market by December 31, 2011.

PMC#4: To conduct a study to substantiate the use of (b) (4) as the (b) (4) (b) (4) and submit the validation study report by December 31, 2011.

PMC#5: To collect data from rabbit pyrogen testing on three lots of thawed and diluted drug substance solution prior to [REDACTED] (b) (4). Submit a final report containing a description of the method, the rabbit pyrogen test results, and an assessment of the impact of [REDACTED] (b) (4) on drug product quality and the drug product manufacturing process by June 30, 2012.

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**SUMMARY:** This review is an addendum to the CMC microbiology review for drug product manufacturing by Anastasia Lolas dated April 27, 2011 and covers the drug product deficiencies identified in the memo by Acting Branch Chief, Dr. Patricia Hughes, dated July 1, 2011. Amendments 0016 (dated 8/18/2011), 0017 (dated 8/30/2011), 0019 (dated 9/30/2011) and 0020 (dated 10/12/2011) contain communications relating to the CMC deficiencies and responses to the CMC information request dated July 11, 2011 for BLA 125359/0. BLA 125359/0 requests approval of Erwinaze for the treatment of acute lymphoblastic leukemia as a substitute for *E.coli* asparaginase. The [REDACTED] (b) (4) [REDACTED] (b) (4) manufactures the drug substance and drug product and the site has an acceptable compliance status.

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(b) (4)

7 PAGES HAVE BEEN WITHHELD IN FULL AS b4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

PMC#3: To provide validation data from the executed protocol for shipping Erwinaze drug product from the (b) (4) to the US market by December 31, 2011.

PMC#4: To conduct a study to substantiate the use of (b) (4) as the (b) (4), (b) (4) and submit the validation study report by December 31, 2011.

PMC#5: To collect data from rabbit pyrogen testing on three lots of thawed and diluted drug substance solution prior to (b) (4). Submit a final report containing a description of the method, the rabbit pyrogen test results, and an assessment of the impact of (b) (4) on drug product quality and the drug product manufacturing process by June 30, 2012.

#### SIGNATURES/DISTRIBUTION LIST

Primary BMAB Reviewer: Kalavati. Suvarna, Ph.D. *KS*

Date: 10/14/2011

Concurring BMAB Team Leader: Patricia Hughes, Ph.D. *PH*

Date: 10/14/2011

Cc: OMPQ/BMAB/Building 51, Suvarna  
OMPQ/BMAB/Building 51, Hughes  
OND/OODP/DBOP/Building 22, Laughner  
OMPQ/BMAB/Building 51, eCTD Files (STN:125359)

Archived File: S:\archive\BLA\125359\125359.0 rev.mem.BLA.DP. addendum.10-14-11.doc



Food and Drug Administration  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
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Silver Spring, MD 20993

**Date:** 30 June 2011  
**To:** Administrative File, STN 125359/0  
**From:** Mary E. Farbman, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB  
**Endorsement:** Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB  
**Subject:** New BLA  
**US License:** #1829  
**Applicant:** EUSA Pharma (USA), Inc.  
**Mfg Facility:** [REDACTED] (b) (4)  
**Product:** Erwinaze® (asparaginase)  
**Dosage:** Sterile lyophilized powder for injection following reconstitution with 0.9% Sodium Chloride Injection USP, supplied in a 3 mL vial (10,000 IU/vial)  
**Indication:** Acute lymphoblastic leukemia (ALL)  
**Due Date:** 02 Aug 2011

**Recommendation for Approvability**

The BLA, as amended, is recommended for approval from a microbiology product quality perspective with the following post-marketing commitments:

Post-marketing commitment #1: Implement the proposed process improvements described in the BLA Amendment #11, dated March 4, 2011, and reassess bioburden and endotoxin limits. Provide bioburden and endotoxin data from three extraction batches.

Post-marketing commitment #2: Include a step to monitor bioburden and endotoxin of CM6 pooled fractions, CM8 pooled fractions, and DEAE pooled fractions after holds longer than 24 hours.

Post-marketing commitment #3: Qualification of the bioburden and endotoxin test methods is not complete:

- a. Complete the qualification of the endotoxin assay using two additional batches of drug substance.
- b. Complete the qualification of the bioburden assay using two additional batches of drug substance.

**Summary**

L-asparaginase is the active enzyme ingredient of Erwinaze, a proposed new drug product indicated for acute lymphoblastic leukemia. The enzyme is produced by a (b) (4) of (b) (4) of *Erwinia chrysanthemi*, a Gram-negative bacterium.

This memo is a review of the microbiology CMC aspects of the drug substance manufacturing process. A separate drug product microbiology quality assessment has been prepared by Anastasia Lolas.

An information request pertaining to microbial control in the drug substance manufacturing process was sent to the sponsor of the BLA, EUSA Pharma, on 16 Feb 2011. The firm responded with an amendment (125359/0/11) filed on 04 Mar 2011 (eCTD #0010). The original submission and Amendment #11 are reviewed here.

A pre-approval inspection of the drug substance and drug product manufacturing facility, (b) (4) was conducted in association with this BLA review. A seventeen-item FDA Form 483 was issued to the firm at the inspection closing. The firm's responses to the FDA Form 483 have been reviewed by a compliance officer in OMPQ/DIDQ, and the firm has been classified as VAI-acceptable.

(b) (4)

**SIGNATURES/DISTRIBUTION LIST**

Primary BMT Reviewer: Mary E. Farbman, Ph.D. *mef* Date: 01 Jul 11  
Concurring BMT Team Leader: Patricia Hughes, Ph.D. *PHS* Date:  
*Qasim*

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- OC/DMPQ/BMT/Building 51, eCTD Files (STN 125359)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Center for Drug Evaluation and Research  
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10903 New Hampshire Ave.  
Silver Spring, MD 20993

**Date:** 01 July 2011  
**To:** Administrative File, STN 125359/0  
**From:** Patricia F. Hughes, Ph.D., Acting Branch Chief, OC/OMPQ/DGMPA/BMAB  
**Through:** Kalavati Suvarna, Ph.D., Peer reviewer, OC/OMPQ/DGMPA/BMAB  
**Subject:** New biologics license application: Summary of Microbiology CMC deficiencies and Post-marketing commitments (PMCs)  
**US License:** #1829  
**Applicant:** EUSA Pharma (USA) Inc.  
**Facility:** DS & DP – [REDACTED] (b) (4)  
**Product:** Erwinaze™ (*Erwinia* L-asparaginase for Injection)  
**Dosage:** Sterile lyophilized powder for injection following reconstitution with 0.9% Sodium Chloride Injection USP, supplied in a 3 mL glass vial (10,000 IU/vial)  
**Indication:** Treatment of acute lymphoblastic leukemia as a substitute for *E. coli* asparaginase  
**Due date:** 02 August 2011

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### RECOMMENDATION FOR APPROVABILITY:

#### CMC Quality Microbiology

The BLA is not recommended for approval based on the CMC microbiology deficiencies identified during the review of the BLA. Six drug product sterility assurance deficiencies should be resolved prior to the approval of the BLA. In addition, six PMCs (three related to drug substance and three related to drug product) are proposed and should be communicated to the applicant. Primary reviews from BMAB of the drug substance and drug product sections of the BLA are attached to this review.

#### CGMP Status of Establishments

The manufacturer of both the drug substance and drug product is [REDACTED] (b) (4). The establishment was inspected by a team of OMPQ/DGMPA/BMAB and OPS/OBP/DTP reviewers on [REDACTED] (b) (4) and a 17 item FDA Form 483 was presented to the manufacturer. [REDACTED] (b) (4) has responded to the observations, which were

evaluated by the Division of International Drug Quality and the responses were deemed acceptable. The establishment is currently acceptable from a GMP perspective.

(b) (4) conducts sterility and endotoxin testing. The testing site was inspected (b) (4) and the initial classification of the site is VAI-acceptable.

(b) (4) performs labeling, packaging and distribution of the drug product and was inspected on (b) (4) and the initial classification is VAI-acceptable.

(b) (4) conducts QC testing for sub-visible particulates in the drug product. This testing lab was last inspected (b) (4) and is acceptable.

A final TB-EER should be submitted 15-30 days prior to the action letter for these sites by the OND RPM.

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**The following is a list of deficiencies identified in the CMC microbiology review of the drug product section of the BLA that should be resolved prior to approval:**

(b) (4)



**The following is a list of PMCs related to drug product manufacturing that should be communicated to the applicant:**

1. Provide data from rabbit pyrogen testing on three lots of thawed and diluted drug substance solution prior to (b) (4). In addition, the applicant should provide a description of the method and an assessment of the results regarding impact on drug product quality and the drug product manufacturing process. The (b) (4) was originally included to remove pyrogens. The rabbit pyrogen data and test results should be submitted in a CBE-0 by a date to be determined.
2. Submit a detailed protocol for method validation and study execution for a physical or chemical container-closure integrity test for samples on stability *in lieu* of sterility testing. Data from studies should be submitted in a PAS by 31 Dec 2011.
3. Provide validation data from the executed protocol for shipping Erwinaze drug product from the (b) (4) to the US market. Submit the data in a CBE-0 supplement by a date to be determined.

**The following is a list of PMCs related to the drug substance manufacturing that should be communicated to the applicant:**

1. Implement the proposed process improvements described in BLA amendment # 11, dated March 4, 2011, and re-assess the bioburden and endotoxin limits. Submit bioburden and endotoxin data from three extraction batches by a date to be determined.
2. Monitor bioburden and endotoxin levels in CM6 pooled fractions, CM8 pooled fractions, and DEAE pooled fractions held for more than 24 hours at scale. Submit data showing that acceptance criteria are met after hold conditions from three runs by a date to be determined.
3. Qualification of the bioburden and endotoxin in-process test methods is not complete.
  - a. Complete the qualification of the endotoxin assay using two additional batches of drug substance and submit the report by a date to be determined.
  - b. Complete the qualification of the bioburden assay using two additional batches of drug substance and submit the report by a date to be determined.

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**Conclusion**

- I. The BLA was reviewed from a microbiology product quality perspective and is not recommended for approval on the basis of deficiencies in sterility assurance. Several PMCs should be communicated to the applicant (see above).
- II. The application was reviewed by an OBP/DTP for CMC product quality.
- III. No additional inspection follow-up items were identified. A final TB-EER should be submitted 15 - 30 days prior to the BLA action date.

**SIGNATURES/DISTRIBUTION LIST**

Acting Branch Chief, BMAB: Patricia F. Hughes, Ph.D.

  


Date:

7/1/11

Concurring BMAB Peer Reviewer: Kalavati Suvarna, Ph.D.

Date:

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Food and Drug Administration  
Center for Drug Evaluation and Research  
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10903 New Hampshire Ave.  
Silver Spring, MD 20993

**Date:** 27 April 2011  
**To:** Administrative File, STN 125359/0  
**From:** Anastasia G. Lolas, Microbiologist, OC/DMPQ/MAPCB/BMT  
**Through:** Patricia Hughes, Ph.D., Team Leader, OC/DMPQ/MAPCB/BMT  
**Subject:** New biologics license application  
**US License:** #1829  
**Applicant:** EUSA Pharma (USA) Inc.  
**Facility:** DS & DP – (b) (4)  
**Product:** Erwinaze™ (*Erwinia* L-asparaginase for Injection)  
**Dosage:** Sterile lyophilized powder for injection following reconstitution with 0.9% Sodium Chloride Injection USP, supplied in a 3 mL glass vial (10,000 IU/vial)  
**Indication:** Treatment of acute lymphoblastic leukemia as a substitute for *E. coli* asparaginase  
**Due date:** 02 August 2011

**Recommendation for Approvability:** BLA STN 125359/0 is not recommended for approval from a microbial control, CMC sterility assurance and microbiology product quality perspective. See page 39 for a list of deficiencies. In addition, the initial recommendation of the pre-license inspection of (b) (4), the drug substance and drug product manufacturing site is non-concur approval.

### Review Summary

EUSA Pharma Inc. submitted a new biologics license application, STN 125359/0 (seq 0000) on 08-Sep-2010 to license Erwinaze™ (*Erwinia* L-asparaginase for Injection) and the associate drug substance and drug product manufacturing processes. This is a rolling submission in eCTD format with Module 3 submitted as the last section of the BLA (seq 0001 submitted 29-Oct-2010). The referenced IND is 290. Pre-BLA meetings were held with the firm in June 2006, September 2009 and December 2009. The BLA was granted priority review status with a user fee date of 03-May-2011. The user fee date was extended to 02-Aug-2011 following the receipt of a major amendment (seq 0008).

Erwinaze is indicated for the treatment of acute lymphoblastic leukemia as a substitute for *E. coli* asparaginase. It contains the enzyme L-asparagine amidohydrolase produced by *Erwinia*

*chrysanthemi*. The drug product is supplied as a sterile, lyophilized powder in a 3 mL glass vial (10,000 IU/vial). The powder is reconstituted with saline prior to administration.

A single facility, the (b) (4), manufactures drug substance and drug product. This facility was inspected (b) (4) by BMT and OBP. There were 17 Form FDA 483 observations and the initial recommendation is VAI – non-concur approval for the BLA until identified issues have been resolved. (b) (4) (b) (4), conducts sterility testing of the drug product. The testing site is under the surveillance program and was inspected in early (b) (4). The previous inspection was conducted in (b) (4). (b) (4) performs labeling, packaging and distribution of the drug product and was inspected by the field on (b) (4) (b) (4). Initial classification is VAI-acceptable. However, there were 9 Form 483 observations.

The following amendments related to CMC product quality microbiology were reviewed: 29-Oct-2010 (seq 0001), 23-Feb-2011 (seq 0008), 04-Apr-2011 (seq 0013) and 22-Apr-2011 (seq 0014). An information request was included in the 74-day letter to provide summary data from the rabbit pyrogen test performed with Erwinaze manufactured using the current proposed commercial process. This information was submitted in sequence 0008. Another information request containing 19 microbiology questions was sent on 10-Mar-2011. Seq 0013 provides the response to these questions.

This review addresses only the Erwinaze drug product and its manufacturing process. A separate microbiology review has been written for the drug substance.

This is an approved drug product in the UK with the name Crisantaspase. Approval was granted in 1985. Development of the manufacturing process began in 1968. The drug product is also marketed in several other countries. However, there are deficiencies that preclude approval of this BLA from a product quality and sterility assurance perspective.

### **Review Narrative**

EUSA Pharma submitted STN 125359/0 (seq 0000) on 08-Sep-2010 to license Erwinaze™ (*Erwinia* L-asparaginase) and the associated drug substance and drug product manufacturing processes. The application is a priority review with an initial PDUFA user fee date of 03-May-2011. The user fee date was extended to 02-Aug-2011 following the receipt of a major amendment on 23-Feb-2011 (seq 0008). The BLA is an electronic submission in CTD format. It is also a rolling BLA with Module 3 submitted as seq 0001 on 29-Oct-2010. The referenced IND is 290. Pre-BLA meetings were held with the firm in June 2006, September 2009 and December 2009.

This review addresses only the Erwinaze drug product and its manufacturing process.

(b) (4)

**A.2 Adventitious Agents Safety Evaluation – Defer to OBP**

**R REGIONAL INFORMATION**

Master and executed batch records are provided in the submission but were not reviewed. Batch records were reviewed during the pre-license inspection. There were observations and recommendations.

**Environmental Assessment**

A claim for categorical exclusion from preparing an Environmental Assessment under 21 CFR 25.31(b) is provided on the grounds that no extraordinary circumstances exist that that would require the preparation of an environmental assessment. Erwinaze is an enzyme, L-asparaginase amidohydrolase, derived naturally from *Erwinia chrysanthemi*. The enzyme catalyzes the reaction of L-asparagine to L-aspartic acid and ammonia. The applicant estimates that approximately

[REDACTED] (b) (4)

The expected introduction concentration into the aquatic environment was calculated significantly less than 1 ppb.

**CGMP Status**

The pre-license inspection of the (b) (4) drug substance and drug product manufacturing facility was conducted [REDACTED] (b) (4) and the initial recommendation is non-concur approval as there were 17 Form 483 observations. [REDACTED] (b) (4) was inspected by ORA on [REDACTED] (b) (4) and resulted in 9 observations. The initial recommendation is VAI-acceptable. [REDACTED] (b) (4) was inspected [REDACTED] (b) (4) and the initial classification is VAI-acceptable. There were 2 observations. Final classification is pending for all 3 sites.

[REDACTED] (b) (4) was inspected in [REDACTED] (b) (4) and has an acceptable compliance status for profiles SVL and SVS.

[REDACTED] (b) (4) was inspected in [REDACTED] (b) (4) and has an acceptable compliance status for profile CTL.

**Conclusion**

- I. The BLA was reviewed from a sterility assurance perspective and microbiology product quality perspective and is not recommended for approval. See page 39 for a list of product quality microbiology deficiencies.
- II. The application should be reviewed by an OBP/DTP reviewer in its entirety.
- III. No additional inspection follow-up items were identified.

**SIGNATURES/DISTRIBUTION LIST**

Primary BMT Reviewer: Anastasia G. Lolas, M.S. 

Date:

4/27/11

Concurring BMT Team Leader: Patricia Hughes, Ph.D. 

Date:

5/13/11

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DMPQ/BMT/Building 51, eCTD Files (STN 125359)

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**PRODUCT QUALITY (Biotechnology)  
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

BLA Number: 125359/0

Applicant: EUSA Pharma, Inc.

Stamp Date: 01-Nov-2010

Established/Proper Name: *Erwinia L-asparaginase*

BLA Type: Priority

On **initial** overview of the BLA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y	
Form 356h completed	Y	
<input type="checkbox"/> including list of all establishment sites and their registration numbers	Y	
Comprehensive Table of Contents	Y	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling:	Y	Only (b) (4)
<input type="checkbox"/> PI –non-annotated	Y N	(b) (4) All other labeling deferred to OBP
<input type="checkbox"/> PI –annotated	Y N	
<input type="checkbox"/> PI (electronic)	Y N	
<input type="checkbox"/> Medication Guide	Y N	
<input type="checkbox"/> Patient Insert	Y N	
<input type="checkbox"/> package and container	Y N	
<input type="checkbox"/> diluent	Y N	
<input type="checkbox"/> other components	Y N	
<input type="checkbox"/> established name (e.g. USAN)	Y N	
<input type="checkbox"/> proprietary name (for review)	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y	
<input type="checkbox"/> legible	Y	
<input type="checkbox"/> English (or translated into English)	Y	
<input type="checkbox"/> compatible file formats	Y	
<input type="checkbox"/> navigable hyper-links	Y	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	Y	
<input type="checkbox"/> summary reports reference the location of individual data and records	Y	
<input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	Y	
Companion application received if a shared or divided manufacturing arrangement	Y N	N/A

**PRODUCT QUALITY (Biotechnology)  
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

<b>CTD Module 2 Contents</b>	<b>Present?</b>	<b>If not, justification, action &amp; status</b>
Overall CTD Table of Contents [2.1]	Y	
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	
<input type="checkbox"/> Drug Substance	Y	
<input type="checkbox"/> Drug Product	Y	
<input type="checkbox"/> Facilities and Equipment	Y	
<input type="checkbox"/> Adventitious Agents Safety Evaluation	Y N	Defer to OBP
<input type="checkbox"/> Novel Excipients	Y N	Defer to OBP
<input type="checkbox"/> Executed Batch Records	Y	
<input type="checkbox"/> Method Validation Package	Y	
<input type="checkbox"/> Comparability Protocols	N	

<b>CTD Module 3 Contents</b>	<b>Present?</b>	<b>If not, justification, action &amp; status</b>
Module Table of Contents [3.1]	Y	
Drug Substance [3.2.S]		
<input type="checkbox"/> general info	Y	
<input type="checkbox"/> nomenclature		
<input type="checkbox"/> structure (e.g. sequence, glycosylation sites)		
<input type="checkbox"/> properties		
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	Y	
<input type="checkbox"/> description of manufacturing process and process control	Y	
<input type="checkbox"/> batch numbering and pooling scheme		
<input type="checkbox"/> cell culture and harvest		
<input type="checkbox"/> purification		
<input type="checkbox"/> filling, storage and shipping		
<input type="checkbox"/> control of materials	Y	
<input type="checkbox"/> raw materials and reagents		
<input type="checkbox"/> biological source and starting materials		
<input type="checkbox"/> cell substrate: source, history, and generation		
<input type="checkbox"/> cell banking system, characterization, and testing		
<input type="checkbox"/> control of critical steps and intermediates	Y	
<input type="checkbox"/> justification of specifications		
<input type="checkbox"/> stability		
<input type="checkbox"/> process validation (prospective plan, results, analysis, and		



**PRODUCT QUALITY (Biotechnology)**  
**FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?	If not, justification, action & status
<ul style="list-style-type: none"> <li>○ Environmental Monitoring Program</li> <li>○ Lyophilizer validation</li> <li>○ Other needed validation data (hold times)</li> <li>□ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)</li> <li>□ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)</li> <li>□ reference standards or materials</li> <li>□ container closure system [3.2.P.7] <ul style="list-style-type: none"> <li>○ specifications (vial, elastomer, drawings)</li> <li>○ availability of DMF &amp; LOAs</li> <li>○ administration device(s)</li> </ul> </li> <li>□ stability <ul style="list-style-type: none"> <li>□ summary</li> <li>□ post-approval protocol and commitment</li> <li>□ pre-approval <ul style="list-style-type: none"> <li>○ protocol</li> <li>○ results</li> <li>○ method validation</li> </ul> </li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Y</li> <li>Y</li> <li>Y</li> <li>Y    N</li> <li>Y</li> <li>Y    N</li> <li>Y    N</li> <li>Y    N</li> <li>Y</li> <li>Y</li> <li>Y</li> <li>Y</li> <li>Y</li> <li>Y</li> </ul>	<ul style="list-style-type: none"> <li>The general program is described in 3.2.A.1</li> <li>Defer to OBP</li> <li>Sterility and bacterial endotoxins only. All other deferred to OBP</li> <li>Defer to OBP</li> <li>Defer to OBP</li> <li>No LOAs for glass vial and stopper DMFs</li> <li>N/A</li> <li>Sterility, container-closure integrity and bacterial endotoxins. All other deferred to OBP</li> </ul>
<ul style="list-style-type: none"> <li>Diluent (vials or filled syringes) [3.2P'] <ul style="list-style-type: none"> <li>□ description and composition of diluent</li> <li>□ pharmaceutical development <ul style="list-style-type: none"> <li>○ preservative effectiveness</li> <li>○ container-closure integrity</li> </ul> </li> <li>□ manufacturers (names, locations, and responsibilities of all sites involved)</li> <li>□ batch formula</li> <li>□ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)</li> <li>□ controls of critical steps and intermediates</li> <li>□ process validation including aseptic</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Y    N</li> </ul>	<ul style="list-style-type: none"> <li>N/A; Diluent not supplied with Erwinaze</li> </ul>



**PRODUCT QUALITY (Biotechnology)**  
**FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

<b>CTD Module 3 Contents</b>	<b>Present?</b>	<b>If not, justification, action &amp; status</b>
<ul style="list-style-type: none"> <li>preparation, sterilization and storage</li> <li>○ procedures and design features to prevent contamination and cross-contamination</li> <li><input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.: <ul style="list-style-type: none"> <li>○ avoidance and control procedures</li> <li>○ cell line qualification</li> <li>○ other materials of biological origin</li> <li>○ viral testing of unprocessed bulk</li> <li>○ viral clearance studies</li> <li>○ testing at appropriate stages of production</li> </ul> </li> <li><input type="checkbox"/> novel excipients</li> </ul>	<ul style="list-style-type: none"> <li>Y</li> <li>Y    N</li> <li>Y    N</li> </ul>	<ul style="list-style-type: none"> <li></li> <li>[to be determined by OBP]</li> <li>[to be determined by OBP]</li> </ul>
USA Regional Information [3.2.R] <ul style="list-style-type: none"> <li><input type="checkbox"/> executed batch records</li> <li><input type="checkbox"/> method validation package</li> <li><input type="checkbox"/> comparability protocols</li> </ul>	<ul style="list-style-type: none"> <li>Y</li> <li>Y</li> <li>N</li> </ul>	
Literature references and copies [3.3]	Y	

<b>Examples of Filing Issues</b>	<b>Yes?</b>	<b>If not, justification, action &amp; status</b>
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	Y	
Includes data demonstrating consistency of manufacture	Y	
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y	
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y	
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y    N	Defer to OBP
Certification that all facilities are ready for inspection	N	No certification but BLA states that sites are available for inspection during the third month of the review cycle as

**PRODUCT QUALITY (Biotechnology)  
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Examples of Filing Issues	Yes?	If not, justification, action & status
		previously discussed with the Agency. Production schedules are provided.
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y    N	Defer to OBP
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> mycoplasma <input type="checkbox"/> sterility	Y    N  Y    N Y    N	Need to ask the applicant Defer to OBP N/A
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y    N	Defer to OBP
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y	

**PRODUCT QUALITY (Biotechnology)  
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?** **Yes**

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

In the early development phase of Erwinaze, pyrogenicity was observed as tested using the rabbit pyrogen test. The drug substance and drug product manufacturing processes have been modified since then. However, it is not clear whether the rabbit pyrogen test has been conducted on drug product manufactured using the proposed commercial process. Clarify whether the rabbit pyrogen test has been conducted at least once to demonstrate that Erwinaze does not contain pyrogenic substances other than bacterial endotoxins. Provide information and summary data for the rabbit pyrogen test in conformance to 21CFR610.13(b).

Mary Farbman, Ph.D. (DS), Anastasia Lolas, M.S. (DP) *AL* 12/6/10  
\_\_\_\_\_  
Product Quality Reviewer(s) Date

Patricia Hughes, Ph.D., BMT Team Leader *PHL* 12/9/10  
\_\_\_\_\_  
Branch Chief/Team Leader/Supervisor Date

*[Signature]* *for RF* 12-14-10  
\_\_\_\_\_  
Division Director Date