

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125359Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: BLA 125359

Supplement Number: _____

NDA Supplement Type (e.g. SE5): _____

Division Name: DBOP

PDUFA Goal Date:
05/03/2011

Stamp Date: 11/1/2010

Proprietary Name: ERWINAZE

Established/Generic Name: L-asparaginase

Dosage Form: powder for solution for injection

Applicant/Sponsor: EUSA (US) Pharma

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
- (2) _____
- (3) _____
- (4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1

(Attach a completed Pediatric Page for each indication in current application.)

Indication: treatment of patients with Acute Lymphoblastic Leukemia (ALL) who have developed hypersensitivity to ^{(b)(4)} E. coli derived asparaginase.

Q1: Is this application in response to a PREA PMR? Yes Continue

No Please proceed to Question 2.

If Yes, NDA/BLA#: _____

Supplement #: _____

PMR #: _____

Does the division agree that this is a complete response to the PMR?

Yes. Please proceed to Section D.

No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

Yes. PREA does not apply. **Skip to signature block.**

No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

Yes: (Complete Section A.)

No: Please check all that apply:

Partial Waiver for selected pediatric subpopulations (Complete Sections B)

Deferred for some or all pediatric subpopulations (Complete Sections C)

Completed for some or all pediatric subpopulations (Complete Sections D)

Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):
 Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients

in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

; Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

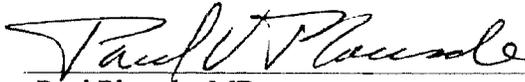
Regulatory Project Manager

(Revised: 6/2008)

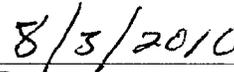
NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Regarding BLA 125,359, Erwinaze®.

I, the undersigned, do hereby certify that EUSA Pharma (USA), Inc., did not use in any capacity the services of any person debarred under subsection (a) and (b) of section 306 of the Food, Drug and Cosmetic Act in connection with this application.



Paul Plourde, MD
Senior Vice President
Global Medical Oncology & US Medical Affairs Head
EUSA Pharma (USA), Inc



Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # BLA # 125359	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: ERWINAZE Established/Proper Name: asparaginase Erwinia chrysanthemi Dosage Form: Powder for Injection		Applicant: EUSA Pharma (USA), Inc. Agent for Applicant (if applicable):
RPM: Erik S. Laughner		Division: DOP2/OHOP
<p>NDA: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>August 2, 2011</u> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR <input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics ²	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)</p> <p>Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Communication Plan <input type="checkbox"/> Submitted in response to a Pediatric Written Request <input type="checkbox"/> ETASU <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input checked="" type="checkbox"/> Yes, dates Product Sheets: 10/18/11 Facility Sheets: 10/20/11
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other ASCO BURST

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

<p>❖ Exclusivity</p>	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
<p>❖ Patent Information (NDAs only)</p>	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
---	--

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	YES
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Approval 11/18/11
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	11/16/11 Final Draft
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	09/08/10
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	ONCASPAR, ELSPAR

³ Fill in blanks with dates of reviews, letters, etc.

<p>Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)</p>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<p>❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</p>	
<ul style="list-style-type: none"> • Most-recent draft labeling 	11/14/11 Final Draft
<p>❖ Proprietary Name</p> <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	11/10/10 Ltr 11/7/11 11/15/10
<p>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</p>	<input checked="" type="checkbox"/> RPM 01/14/11 <input checked="" type="checkbox"/> DMEPA 05/05/11 <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC 05/02/11 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews MHT 04/11/11 OBP 06/17/11
Administrative / Regulatory Documents	
<p>❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</p>	12/14/10 Mtg Memo and Filing Memo
<p>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</p>	<input checked="" type="checkbox"/> Not a (b)(2)
<p>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</p>	<input checked="" type="checkbox"/> Not a (b)(2)
<p>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</p>	<input type="checkbox"/> Included
<p>❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</p>	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<p>❖ Pediatrics (<i>approvals only</i>)</p> <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: ORPHAN • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

<p>❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)</p>	<p><input checked="" type="checkbox"/> Verified, statement is acceptable</p>
	<p>11/16/11 IR (Labeling) 11/14/11 IR (Labeling) 11/09/11 IR (Labeling PMR/PMC) 11/2/11 TCON 10/27/11 IR #2 (Labeling) 10/27/11 IR (PMR) 10/17/11 IR (PMR) 10/14/11 IR (PMC) 10/07/11 IR (Labeling) 10/03/11 TCON 09/28/11 TCON 09/20/11 TCON 09/13/11 IR 09/01/11 IR 08/26/11 IR 08/24/11 TCON 08/17/11 TCON 08/16/11 IR 08/05/11 TCON 08/04/11 IR 07/15/11 TCON 07/14/11 TCON 07/14/11 IR 07/11/11 IR 07/11/11 IR 07/07/11 TCON</p>
<p>❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)</p>	<p>06/23/11 F/F Mtg (Special) 05/27/11 TCON 05/03/11 TCON 05/03/11 TCON 04/07/11 IR 04/07/11 TCON 03/18/11 IR 03/15/11 IR 03/14/11 IR 03/11/11 IR 03/10/11 IR 03/08/11 IR 03/07/11 TCON 03/04/11 TCON 03/04/11 Major Amend LTR 02/16/11 IR#2 02/16/11 IR 02/15/11 IR 02/01/11 IR 01/28/11 IR 01/28/11 IR 01/14/11 74-Day LTR 01/12/11 IR 01/06/11 IR 01/03/11 IR 12/28/10 Filing LTR 12/21/10 TCON</p>

	12/16/10 TCON 12/16/11 IR 12/14/10 IR 12/10/10 IR 11/23/10 IR 11/19/10 Ack. LTR 11/16/10 IR 11/12/10 IR 11/03/10 IR 10/28/10 IR LTR 09/28/10 IR
❖ Internal memoranda, telecons, etc.	11/18/11 Memo Correction AP ltr 10/26/11 Wrap-up Mtg 10/05/11 Sixth Labeling Mtg 09/29/11 Fifth Labeling Mtg 09/23/11 Monthly Team Mtg 05/17/11 Monthly Team Mtg 04/12/11 Monthly Team Mtg 03/04/11 Fourth Labeling Mtg 03/03/11 Third Labeling Mtg 02/23/11 Second Labeling Mtg 02/18/11 First Labeling Mtg 02/15/11 Monthly Team Mtg 02/11/11 Mid-Cycle Mtg 01/07/11 Monthly Team Mtg 12/15/10 Review Designation 11/17/10 Planning Mtg
❖ Minutes of Meetings	
<ul style="list-style-type: none"> Regulatory Briefing (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 12/07/09 (note: preliminary comments sent on 12/7/09; Sponsor cancelled 12/10/09 meeting) 09/03/09
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
<ul style="list-style-type: none"> 48-hour alert or minutes, if available (<i>do not include transcript</i>) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/17/11
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/15/11
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/07/11
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 16 PMCs and 6 PMRs

Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (indicate date for each review)	TL is CDTL; see CDTL review
• Clinical review(s) (indicate date for each review)	10/31/11 Addendum 06/17/11 12/21/10 Filing Checklist
• Social scientist review(s) (if OTC drug) (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (indicate date of review/memo)	See page 15 of 06/17/11 clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review)	<input type="checkbox"/> None 06/03/11 (immuno assay)
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and Supporting Statement (indicate date(s) of submission(s)) • REMS Memo(s) and letter(s) (indicate date(s)) • Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review) 	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	<input type="checkbox"/> None requested 03/07/11
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None co-signed 10/24/11 addendum co-signed 05/25/11 review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None co-signed 10/24/11 addendum co-signed 05/25/11 review
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 10/24/11 addendum 05/25/11 review 12/16/10 Filing Checklist Addn: 03/16/11 IRT/QT
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input type="checkbox"/> None 09/30/11 07/13/11 03/16/2011

⁵ Filing reviews should be filed with the discipline reviews.

Nonclinical		<input type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) (indicate date for each review)		<input type="checkbox"/> None 10/28/11
• Supervisory Review(s) (indicate date for each review)		<input type="checkbox"/> None 10/27/11
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)		<input type="checkbox"/> None 07/12/11 12/14/10 Filing Checklist
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)		<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)		<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting		<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)		<input checked="" type="checkbox"/> None requested
Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) (indicate date for each review)		<input type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)		<input type="checkbox"/> None 11/16/11 Executive Summary (Beaucage) 10/26/11 (Beaucage)
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)		<input type="checkbox"/> None 11/15/11 (Cieslak) Proper Name Review 10/28/11 (Spiridonov) addendum 10/24/11 (Cieslak) addendum 10/21/11 (Ausin) addendum 06/21/11 (Spiridonov) 06/20/11 (Ausin) 06/20/11 (Cieslak) 12/15/10 Filing Checklist
❖ Microbiology Reviews		<input type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)		10/14/11 Addendum 07/01/11 (Branch Chief) 06/30/11
<input checked="" type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (indicate date of each review)		04/27/11 12/14/10 Filing Checklist
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)		<input checked="" type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	see pg 4; 11/16/11 Executive Summary (Beaucage)
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input checked="" type="checkbox"/> Not applicable
<input checked="" type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: 10/28/11 Acceptable 10/26/11 Request <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

RPM FILING REVIEW
(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # BLA# 125359	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Erwinaze Established/Proper Name: Not decided (applicant in consultation with FDA) Dosage Form: Powder for Solution for Injection Strengths: 10,000 IU/vial		
Applicant: EUSA Pharma (USA), Inc. Agent for Applicant (if applicable):		
Date of Application: 11/01/10 (complete date of rolling submission- PDUFA clock triggered) Date of Receipt: 11/01/10 Date clock started after UN:		
PDUFA Goal Date: 05/03/11	Action Goal Date (if different):	
Filing Date: 12/31/10	Date of Filing Meeting: 12/14/10	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): Treatment of patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to ^{(b)(4)} <i>E. coli</i> -derived asparaginase.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority	<input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input checked="" type="checkbox"/> Fast Track <input checked="" type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)	

Other:	<input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 290				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application: <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</i>				

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm				
If yes, please list below:				
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>				
Exclusivity	YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm		X		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?				
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance ¹ ? If not , explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including: <input checked="" type="checkbox"/> legible English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.	X			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? <i>If yes, date consult sent to the Controlled Substance Staff:</i>			X	
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #			X	

Forms and Certifications				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature? <i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>	X			
Are all establishments and their registration numbers listed on the form/attached to the form?				
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?			X	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? <i>Forms must be signed by the APPLICANT, not an Agent.</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	X			Fixed by Sponsor as a result of 10/28/10 IR letter while still under rolling review.
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>) <i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i> <i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	X			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		X		ORPHAN
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>			X	
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>			X	
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>			X	
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>				

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>	X			
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? <i>(send WORD version if available)</i>			X	
REMS consulted to OSE/DRISK?			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				

Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	X			MHT, QT-IRT, OSE, DSI

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 09/03/09 clinical pre-BLA, 12/7/09 CMC pre-BLA preliminary comments (meeting cancelled by Sponsor) <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

¹<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 14, 2010

BLA/NDA/Supp #: STN 125359

PROPRIETARY NAME: Erwinaze

ESTABLISHED/PROPER NAME: Not yet chosen

DOSAGE FORM/STRENGTH: Powder for Solution for Injection; 10,000 IU/vial

APPLICANT: EUSA Pharma (USA), Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to (b) (4) (b) (4) *E. coli*-derived asparaginase.

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Erik Laughner	Y
	CPMS/TL:	Karen Jones	Y
Cross-Discipline Team Leader (CDTL)	Kaushik Shastri		
Clinical	Reviewer:	Patricia Dinndorf	Y
	TL:	Suzanne Demko	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
OTC Labeling Review (for OTC products)	Reviewer:		
	TL:		
Clinical Microbiology (for antimicrobial products)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Jun Yang	Y
	TL:	Hong Zhao	Y
Biostatistics	Reviewer:	N/A PK endpoint	
	TL:	N/A PK endpoint	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Dubravka Kufrin	Y
	TL:	Anne Pilaro	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	Faruk Sheikh	N
	TL:	Suzanne Kirshner	Y
Product Quality (CMC)	Reviewer:	Jacek Cieslak	Y
	TL:	Serge Beaucage	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review (<i>for BLAs/BLA supplements</i>)	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Anastasia Lolas Mary Farbman	Y N
	TL:	Patricia Hughes	Y
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		

Other reviewers		
Other attendees	Jeff Summers, DDS Grace Carmouze, sRPM	

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable Initial comments in 10/28/10 IR letter while still under rolling review.
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>Comments:</p> <ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: Early December <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined <p>Reason:</p> <ul style="list-style-type: none"> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>

<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments: Assays not yet validated, Applicant working on. Patient samples from study are archived. Will be PMRs if approval action.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments: Handled by DTP review team</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments: This is a NME. The Facility group will do the "initial compliance check" to determine inspection needs.</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review (BLAs/BLA supplements only)</u></p> <p>Comments: OBP Reviewer will provide review during review cycle (after mid-cycle)</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Richard Pazdur, OODP Director

21st Century Review Milestones To be Followed Per Review Planner/GRMP Calculator

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>

ACTIONS ITEMS

<input checked="" type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.



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

Memorandum

Date: 11/18/11 *ESC 11/18/11*

From: Erik Laughner, RPM DOP2/OHOP/CDER/FDA

Subject: BLA STN 125359 (Erwinaze); Correction to Approval Letter 11/18/11

The Office (OHOP) sent an initial BLA approval letter to the company on 11/18/11 (see attached to this memo). That letter contained an error in the reporting year under postmarketing commitment number 8. **A replacement letter acknowledging the error and containing the correct reporting date was provided to the applicant on the same date.** That replacement letter became the official approval letter. This memo documents sending the "first" approval letter for the record as it was received by the applicant.

From: Laughner, Erik
Sent: Friday, November 18, 2011 8:31 AM
To: 'Paul Plourde'
Subject: BLA STN 125359; FDA Approval Letter with Attached Labeling



L25359 AP LTR.PDF
(1 MB)

Good Morning Paul,

Please find FDA letter with attached labeling. Please confirm receipt and ability to open.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products (OHOP)
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

If you have received this message in error, do not use, disclose, reproduce, or distribute this message (including any attachments) and notify me immediately. Thank you.



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

Memorandum

Date: 11/16/11

SL 11/16/11

From: Erik Laughner, RPM DOP2/OHOP/CDER/FDA

Subject: BLA STN 125359 (Erwinaze); Minor Revisions to Package Insert

From: Laughner, Erik
Sent: Wednesday, November 16, 2011 9:11 AM
To: 'Paul Plourde'
Subject: STN 125359 Erwinaze; 111611 labeling revisions
Importance: High

Paul,

The attached redline of the package insert reflects the final changes we would like incorporated.

If you have any questions, please let me know.

Otherwise, please clean up and provide a final clean version which will accompany the action letter. You can also submit the final amendment to the BLA file.

Erik



REDLINE Draft PI
STN 125359 1...

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products (OHOP)
CDER/FDA
301-796-1393

erik.laughner@fda.hhs.gov

<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

If you have received this message in error, do not use, disclose, reproduce, or distribute this message (including any attachments) and notify me immediately. Thank you.

8 PAGES OF DRAFT LABELING HAVE BEEN WITHHELD IN FULL AS b4 (CCI/TS)
IMMEDIATELY FOLLOWING THIS PAGE



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

Memorandum

Date: 11/14/11

ESL
11/14/11

From: Erik Laughner, RPM DOP2/OHOP/CDER/FDA

Subject: BLA STN 125359 (Erwinaze); Minor Revisions to Carton/Container



Proposed ERW
Labels 111411 FDA.d

From: Laughner, Erik
Sent: Monday, November 14, 2011 8:22 AM
To: 'Paul Plourde'
Subject: STN 125359; Carton/Container
Importance: High

Good Morning Paul,

Thanks for your email. Hope you had a good weekend.

With respect to the carton/containers, the route must appear below the tradename not the Units.

See attached redline- you can accept all changes.

Also, I have deleted the "picture" of the vial as we don't need that anymore- we just needed it for our own understanding how the label would wrap around the vial.

Erik



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

Memorandum

Date: 11/09/11

From: Erik Laughner, RPM DOP2/OHOP/CDER/FDA

Subject: BLA STN 125359 (Erwinaze); Minor Revisions to PMCs/PMRs ; FDA
proposed labeling ; package insert ; carton/container

From: Laughner, Erik
Sent: Wednesday, November 09, 2011 2:09 PM
To: 'Paul Plourde'
Subject: STN 125359; FDA PMC, PMR, Carton/Container, Package Insert Revisions
Importance: High

Hello Paul,

Attached are 2 files:

Document one contains the slightly revised PMRs/PMCs which now indicate only the Month/year (no specific day). Also, the PMCs where applicable provide the type of submission that should be provided to the BLA file. Document one also contains the minor revisions needed to the carton/container labels.



110911
MR_CARTON_CONT

Document two is a clean version (with a couple of comments) of the package insert with the new insertion of the proper name. A few minor grammar/formatting changes were made. I think I have replaced all the "XXXXX" where applicable. Please verify.



FDA Proposed Draft
Label STN 1...

The proposed submission date to provide these back to me as a formal amendment to the BLA is 11/14. Please confirm receipt.

Sincerely,

Erik
Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products (OHOP)
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

If you have received this message in error, do not use, disclose, reproduce, or distribute this message (including any attachments) and notify me immediately. Thank you.



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

Memorandum

Date: November 9, 2011
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: FDA Request for Information; BLA STN 125359 (Erwinaze); FDA minor Revisions to PMRs, PMCs and Carton/Container Labels

FDA REVISED LIST OF PMR/PMCs:

Note: The proposed month of submissions are now only cited, the actual date is not required. FDA assumes that the "due date" will be the last day of any given month. Where relevant, the type of expected submission has also been provided for the PMCs.

POSTMARKETING REQUIREMENTS

(b) (4)

11 PAGES OF DRAFT LABELING HAVE BEEN WITHHELD IN FULL AS b4 (CCI/TS)
IMMEDIATELY FOLLOWING THIS PAGE



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

Memorandum

Date: November 2, 2011 ESL 11/2/11
From: Erik Laughner, RPM DOP2/OHOP/CDER/FDA
Subject: EUSA Pharma (STN 125359/0); tcon regarding assignment of Proper Name

FDA Attendees:

Erik Laughner, RPM DOP2
Patricia Keegan, Director DOP2
Maryll Toufanian, Attorney, OCC
Leah Christl, Associate Director for Biosimilars, OND

EUSA Attendees:

Paul Plourde	Erwinaze Project leader
Tim Corn	Chief Medical Officer
Bill Bennett	Head of QA and Regulatory
Harriette Nadler	Regulatory

DISCUSSION: FDA called EUSA Pharma to inform them of a decision to assign the Proper Name: asparaginase *Erwinia chrysanthemi*. This name would be reflected in the final draft labeling (package insert, container/carton) and the action letter. FDA noted that EUSA Pharma could continue their discussions with USAN on naming. FDA would however, need a waiver from EUSA Pharma granting permission to speak with USAN on the assignment of the Proper Name. FDA could not comment at the moment the next steps/scenario if USAN should ultimately assign a different name to what FDA has designated for purposes of this BLA application. EUSA acknowledged the issue and agreed that if a waiver was granted for FDA, they would provide to the BLA application.



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

Memorandum

Date: 10/27/11

ESL
10/27/11

From: Erik Laughner, RPM DOP2/OHOP/CDER/FDA

Subject: BLA STN 125359 (Erwinaze); FDA proposed labeling ; package insert

From: Laughner, Erik
Sent: Thursday, October 27, 2011 3:55 PM
To: 'Paul Plourde'
Subject: STN 125359; Erwinaze 10/27/11 FDA label revisions

Hello Paul,

Here are our latest revisions to the package insert. Please review and provide a revised label (addressing the content and format comments) back to me by next Tuesday 11/1. Please follow-up with a formal amendment to the BLA file.

It is my intention that we will only then need one final minor revision round which can incorporate the "proper name". We are trying to resolve that issue within the next week.

Please confirm receipt.

Thanks,

Erik



102711 FDA
roposed Draft Labe.

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products (OHOP)
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

If you have received this message in error, do not use, disclose, reproduce, or distribute this message (including any attachments) and notify me immediately. Thank you.

8 PAGES OF DRAFT LABELING HAVE BEEN WITHHELD IN FULL AS b4 (CCI/TS)
IMMEDIATELY FOLLOWING THIS PAGE



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

Memorandum

Date: 10/27/11

ek
10/27/11

From: Erik Laughner, RPM DOP2/OHOP/CDER/FDA

Subject: BLA STN 125359 (Erwinaze); FDA proposed Immuno and Nonclinical PMRs



Attachment 4



Attachment 3

Immunogenicity PMR. Nonclinical PMR Final.

From: Laughner, Erik

Sent: Thursday, October 27, 2011 10:49 AM

To: 'Paul Plourde'

Subject: STN 125359; FDA PMR Comments

Hello Paul,

Please see 2 edits to the proposed PMRs in terms of dates. Let me know if you are in agreement and we can consider the PMRs essentially finalized. The PMCs you provided were found to be acceptable.

Thanks,

Erik



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

Memorandum

Date: October 26, 2011 *ESC 10/26/11*
From: Erik Laughner, DOP2/OHOP/CDER
Subject: BLA STN 125359 Erwinaze; Wrap-Up Team Meeting

Regulatory Management

Erik Laughner
Patricia Keegan (Director, DBOP)

OSI

Mike Skelly

Clinical

Patricia Dinndorf
Suzanne Demko (TL)

Nonclinical

Dubravka Kufrin
Anne Pilaro (TL)

Clinical Pharmacology

Jun Yang
Hong Zhao (TL)

Facilities

Kalavati Suvarna

Product

Nikolay Spiridonov
Cristina Ausin
Jacek Cieslak
Serge Beaucage
Susan Kirshner (immunogenicity TL)
Faruk Sheikh (immunogenicity)
Kim Rains (OBP Labeling Reviewer)

OSE

Sue Kang
Robert Pratt
Corrine Kullick

OPDP (formerly DDMAC)

Carole Broadnax

Discussion: Participants were present from all disciplines. This review wrap-up meeting reviewed any remaining items to complete prior to taking an action on the BLA. In addition, OSE attended and was briefed by the Division on the overall safety, efficacy and quality of this drug and its intended use.



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

Memorandum

Date: 10/17/11 ^{ESL} 10/17/11
From: Erik Laughner, RPM DOP2/OHOP/CDER/FDA
Subject: BLA STN 125359 (Erwinaze); FDA proposed Immuno and Nonclinical PMRs

From: Laughner, Erik
Sent: Monday, October 17, 2011 9:26 AM
To: 'Paul Plourde'
Subject: STN 125359; PMRs for Immunogenicity and Nonclinical Repro-Tox
Importance: High

Hello Paul,

See proposed PMRs for immunogenicity and nonclinical evaluation. Please review and provide dates as noted for each PMR.

Please confirm receipt.

Sincerely,

Erik



101711 Nonclinical
and Immuno ...

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products (OHOP)
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

If you have received this message in error, do not use, disclose, reproduce, or distribute this message (including any attachments) and notify me immediately. Thank you.



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

Memorandum

Date: October 17, 2011
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: FDA Request for Information; BLA STN 125359 (Erwinaze); Nonclinical and Immunogenicity PMRs

The following nonclinical PMRs are proposed:

PMR#1: To conduct non-clinical embryofetal development and toxicity (EFT; ICH S5(R2) Harmonized Segment C) studies of ERWINAZE in rats and rabbits. The final protocols for the EFT studies will be submitted by (Month/Day/Year), the studies will be completed by (Month/Day/Year), and the final study reports will be submitted by (Month/Day/Year).

PMR#2: To conduct non-clinical fertility and early pregnancy (Segment I; ICH S5(R2) Harmonized Segment A-B) studies of ERWINAZE in rats. The final protocols for the Segment I toxicity studies will be submitted by (Month/Day/Year), the studies will be completed by (Month/Day/Year), and the final study reports will be submitted by (Month/Day/Year).

PMR#3: To conduct non-clinical peri-postnatal developmental (PPND; Segment III; ISC S5(R2) Harmonized Segment D-F) studies of ERWINAZE in rats. The final protocols for the Segment III PPND toxicity studies will be submitted by (Month/Day/Year), the studies will be completed by (Month/Day/Year), and the final study reports will be submitted by (Month/Day/Year)."

The following immunogenicity PMRs are proposed:

PMR#4: To develop a validated, sensitive, and accurate assay for the detection of binding antibodies to ERWINAZE, including procedures for accurate detection of antibodies to ERWINAZE in the presence of ERWINAZE levels that are expected to be present in the serum at the time of patient sampling. A summary of the validation exercise including supporting data, a summary of the development data supporting assay suitability for parameters not assessed in the validation exercise, and the assay SOP will be provided to FDA.

- Final report submission: (Month/Day/Year)

PMR#5: To develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to ERWINAZE, including procedures for accurate detection of neutralizing antibodies to ERWINAZE in the presence of ERWINAZE levels that are expected to be present in the serum at the time of patient sampling. A summary of the validation exercise including supporting data, a summary of the development data supporting assay suitability for parameters not assessed in the validation exercise, and the assay SOP will be provided to FDA.

- Final report submission: (Month/Day/Year)

PMR#6: To conduct an assessment of anti-drug antibody (ADA) binding response and neutralizing ADA response to ERWINAZE with validated assays (required under PMR 4 and 5) capable of sensitively detecting ADA responses in the presence of ERWINAZE levels that are expected to be present at the time of patient sampling. The ADA response will be evaluated in all archived sampling time points available from all patients in the COG Study AALL07P2.

- Final report submission: (Month/Day/Year)



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

Memorandum

Date: 10/14/11

SS
10/14/11

From: Erik Laughner, RPM DOP2/OHOP/CDER/FDA

Subject: BLA STN 125359 (Erwinaze); FDA proposed CMC PMCs

From: Laughner, Erik
Sent: Friday, October 14, 2011 8:48 AM
To: 'Paul Plourde'
Subject: STN 125359; FDA Proposed list of CMC PMCs
Importance: High

Hello Paul,

Please see the list of CMC PMCs for review/concurrence. Please note that the product group has added 2 new proposed PMCs for review and requested dates be provided.

If you can review with your team and provide back to me by next Wednesday (10/20), I would appreciate.

Please confirm receipt.

Erik



101411 CMC PMCs
Memo.doc (73 ...)

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products (OHOP)
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

If you have received this message in error, do not use, disclose, reproduce, or distribute this message (including any attachments) and notify me immediately. Thank you.



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

Memorandum

Date: October 14, 2011
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: FDA Request for Information; BLA STN 125359 (Erwinaze); CMC (Product and Facility) PMCs

The following product and facility PMCs are provided for review/concurrence. The two product PMCs highlighted in red are new ones that FDA wishes EUSA to perform and propose dates.

FACILITY 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 (b) (4) to the US market by December 31, 2011.

PMC#4: To conduct a study to substantiate the use of (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.

PMC #6: 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 July 31, 2012.

PMC #7: 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 November 30, 2012.

PMC #8: Qualification of bioburden and endotoxin in-process test methods:

- a. Complete the qualification of the endotoxin assay using two additional batches of drug substance and submit the report by July 31, 2012.
- b. Complete the qualification of the bioburden assay using two additional batches of drug substance and submit the report by July 31, 2012.

PRODUCT PMCs

PMC #1: To review the specifications for all release and stability test methods when the manufacture of a statistically significant number of Erwinaze DS and DP lots is completed. The analysis together with any revised release and stability specifications will be submitted by (month, day, year).

PMC #2: To validate hold times for each DS process intermediate, where applicable, in order to demonstrate that the quality of Erwinaze DS is not affected. This study should include a worst case hold scenario, defined by the cumulative maximal time for each hold step along with an evaluation of the purity and potency of process intermediates and of the resulting DS. The complete hold times validation report and supporting test results will be submitted by (month, day, year).

PMC #3: To increase the assay sensitivity for SDS-PAGE. The revised assay together with the validation report and supporting test results will be submitted by December 31, 2011.

PMC #4: To perform SEC and AUC testing in a side-by-side analysis of Erwinaze DS samples that have been subjected to stress conditions. Results of these studies will be submitted by March 31, 2012.

PMC #5: To provide a revised protocol for qualification of the current and future Erwinaze reference standards by December 31, 2011.

PMC #6: To submit an experimental plan for evaluating L-asparagine, as the substrate for measuring the K_m and k_{cat} of Erwinaze DS and DP, by December 31, 2011.

PMC #7: To perform a risk assessment of the impact sub-visible particles may have on the quality, clinical safety and efficacy of Erwinaze DP, and propose a strategy to control this risk by December 31, 2011.

PMC #8: To revise the peptide mapping method used for DS and DP release testing in order to enable chromatographic base-line resolution of most peptide fragments while accounting for ~98% of the protein sequence. The revised assay together with the validation report will be submitted by September 30, 2012.



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

Memorandum

Date: 10/07/11

ESL
10/07/11

From: Erik Laughner, RPM DOP2/OHOP/CDER/FDA

Subject: BLA STN 125359 (Erwinaze); FDA proposed labeling ; package insert and carton/container/vial

From: Laughner, Erik
Sent: Friday, October 07, 2011 11:07 AM
To: 'Paul Plourde'
Subject: STN 125359; FDA Proposed Labeling Revisions
Importance: High

Hello Paul,

Please see FDA's proposed package insert labeling:



100711 FDA
roposed Draft Labe.

This package insert is provided back to you as a clean word version with FDA comments. Please carefully review the proposed label with your team and verify for accuracy as well as correcting for any PLR formatting, indentation, font, cross-reference etc.

Please provide a revised label containing any necessary/suggested revisions back to me as a word document (both clean and track-changed) by October 19.

I expect that one additional round of minor labeling edits will occur (hopefully also finalizing the Proper Name issue).

Once we are OK with the word label, you can follow-up with the SPL file.

Please see the FDA review of the carton/container/vial:



100711 FDA
'roposed carton_co..

Please provide revised color mock-ups of the carton/container/vial by October 19. I expect that one additional round of minor carton/container/vial labeling edits will occur (hopefully also finalizing the Proper Name issue).

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products (OHOP)
CDER/FDA

301-796-1393

erik.laughner@fda.hhs.gov

<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

If you have received this message in error, do not use, disclose, reproduce, or distribute this message (including any attachments) and notify me immediately. Thank you.

12 PAGES OF DRAFT LABELING HAVE BEEN WITHHELD IN FULL AS b4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE



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

Memorandum

Date: October 5, 2011 ^{Erk} 10/05/11
From: Erik Laughner, DOP2/OHOP/CDER
Subject: BLA STN 125359 Erwinaze; Sixth Labeling Meeting- Team Wrap-Up

Regulatory Management

Erik Laughner
Patricia Keegan (Director, DOP2)

Nonclinical

Anne Pilaro (TL)
Dubravka Kufrin

Clinical

Patricia Dinndorf
Suzanne Demko (CDTL)

Clinical Pharmacology

Jun Yang
Hong Zhao

Product

Cristina Ausin
Serge Beaucage
Jacek Cieslak

OSE

Loretta Holmes

DDMAC

Carole Broadnax

Discussion: This labeling meeting was convened with the primary team as well as OSE and DDMAC consult reviewers to perform final review of entire draft FDA label prior to sending to applicant.



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

Memorandum

Date: October 3, 2011 *SEL 10/3/11*
From: Erik Laughner, RPM DOP2/OHOP/CDER/FDA
Subject: EUSA Pharma (STN 125359/0); tcon regarding facility issues

FDA Attendees:

Kalavati Suvarna, Patricia Hughes, Erik Laughner

Applicant Attendees:

EUSA

Paul Plourde Erwinase Project Leader
Tim Corn Chief Medical Officer

(b) (4)

BACKGROUND: FDA requested a brief tcon to discuss the Applicant's recent response on the (b) (4) validation report.

DISCUSSION: FDA noted that they had reviewed EUSA's response to the September 13, 2011 information request regarding the (b) (4) validation. FDA noted that it was typical that these validations were completed prior to a BLA approval and requested clarification on the proposed December 2011 timeframe for completion under a PMC. EUSA Pharma acknowledged and noted that in addition to the 6-8 weeks to complete the validation by the contractor, additional time was needed to actually manufacture the (b) (4) as they were a custom part for this drug. EUSA Pharma noted that the proposed December deadline was chosen to ensure meeting the PMC target date and that it was likely the report could be submitted sooner.

In regards to the recent September 30, 2011 CMC amendment, FDA noted that a reason was not provided for the discarded vials in the media fill runs. EUSA Pharma noted that vials found broken/damaged were discarded. This would include vials that were jammed on the fill lines. FDA acknowledged and requested that EUSA Pharma provide this information to the BLA.

EUSA Pharma confirmed that the medial fill simulations were performed for the entire process and media was (b) (4).

FDA noted that the non-conformances observed during environmental monitoring (EM) performed during the 2011 media fills were concerning. The organisms identified from settle plates and operator gowns were of human origin suggesting that the environment for (b) (4)

(b) (4) was not in control. FDA requested that the locations of samples with EM excursions and corrective actions taken to address the non-conformances be submitted to the BLA. EUSA Pharma acknowledged and agreed to provide this information to the BLA.

FDA confirmed that the proposed shipping validation protocol was acceptable and requested that EUSA Pharma provide a final date for submission of the report as a PMC. FDA requested that as a number of these proposed PMCs had December deadlines, EUSA Pharma should re-align the dates to one date and submit as many of these reports as possible as one BLA correspondence.

EUSA Pharma confirmed that the above information requests could be provided to the BLA as an amendment within one week and that an email desk copy would also be provided to expedite delivery to the FDA review staff.



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

Memorandum

Date: September 29, 2011 수 07/29/11
From: Erik Laughner, DOP2/OHOP/CDER
Subject: BLA STN 125359 Erwinaze; Fifth Labeling Meeting

Regulatory Management

Erik Laughner
Patricia Keegan (Director, DOP2)
Greg Reaman

Clinical

Patricia Dinndorf
Suzanne Demko (CDTL)

Clinical Pharmacology

Jun yang
Hong Zhao

Discussion: This labeling meeting was convened to discuss the “Clinical Pharmacology” and “Clinical Studies” section of the USPI based on recent re-analysis of pharmacokinetic samples.



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

Memorandum

Date: 09/28/11 ESC 09/28/11
From: Erik Laughner, RPM DOP2/OHOP/CDER/FDA
Subject: EUSA Pharma (STN 125359/0); tcon regarding BLA review Status

DISCUSSION: I returned a message from Paul Plourde regarding an update to the FDA review of the BLA. I noted that the clinical pharmacology group had determined that the new PK data was adequate to demonstrate ERWINAZE activity for the label. Paul acknowledged and noted that he had been informed that [REDACTED] (b) (4) had been inspected this past Monday by FDA and that there were no adverse findings. I acknowledged and noted that the Division was still waiting on the final report from the inspection. I also noted that the CMC team was overall satisfied with the responses thus far provided by EUSA Pharma. The team would have to review the final CMC which was targeted for September 30th. Paul acknowledged. A number of PMCs/PMRs would have to be negotiated as well.

I noted that the review team had met late last week and based on the remaining issues to wrap-up for the action, a target date of mid/late November was set. I also indicated that the Division was meeting with the various review groups next week to complete the labeling revisions to the package insert and I anticipated that I could provide the draft label along with draft carton/container labeling the following week. EUSA Pharma would be instructed to review and provide a response back within 7-10 days. [REDACTED] (b) (4)

Paul continued to express concern on the USAN review of the Proper Name. I noted that as the review was likely to be completed soon, he should wait to hear from them and contact me to discuss next steps. Paul acknowledged.



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

Memorandum

Date: September 23, 2011 09/23/11 ESL
From: Erik Laughner, DOP2/OHOP/CDER
Subject: BLA STN 125359 Erwinaze; Standing Monthly Team Meeting

Regulatory Management

Erik Laughner
Patricia Keegan (Director, DBOP)

Clinical

Patricia Dinndorf
Suzanne Demko (TL)

Nonclinical

Dubravka Kufirin
Anne Pilaro (TL)

Clinical Pharmacology

Jun Yang
Hong Zhao (TL)

Facilities

Mary Farbman
Kalavati Suvarna
Patricia Hughes (TL)

Product

Nikolay Spiridonov
Cristina Ausin
Jacek Cieslak
Serge Beaucage
Susan Kirshner (immunogenicity TL)
Kim Rains (OBP Labeling Reviewer)

OSE

Sue Kang

OSI

Michael Skelly

Discussion: Participants were present from all disciplines. This monthly standing meeting provided reviewers/teams opportunity to discuss review status of BLA and set new goal for taking a regulatory action.



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

Memorandum

Date: 09/20/11 *SL 09/20/11*

From: Erik Laughner, RPM DOP2/OHOP/CDER/FDA

Subject: EUSA Pharma (STN 125359/0); tcon regarding submission of CMC and clinical deficiencies and USAN review of proper name

DISCUSSION: Paul Plourde called to update FDA on the submission of the CMC information needed to resolve the pre-approval deficiencies. The final CMC piece was on target for a September 30th submission to FDA. I acknowledged and noted that the new clinical pharmacology data from (b) (4) was under review by the clinical pharmacology group and that I should expect feedback within a few days. Paul indicated continuing concern with the lack of an agreed Proper Name. USAN had not yet completed its review. I acknowledged this process had been dragged out too long and advised that USAN should complete the ballot process over the next few weeks. Paul should call the Division at that point to ensure we are then in agreement on the selection of the Proper Name.



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

Memorandum

Date: 09/13/11 *εα 09/13/11*

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: BLA STN 125359 (Erwinaze); Information Request

From: Laughner, Erik
Sent: Tuesday, September 13, 2011 12:32 PM
To: 'Paul Plourde'
Subject: STN 125359 (Erwinaze); Information Request

Paul,

We have the following information requests:

Report R1WES0031008 (Appendix 4) from (b) (4) was provided to support validation of (b) (4). Please provide the following additional information:

1. The initial validation study report for (b) (4)
2. Summary data to support continued effectiveness of the (b) (4), namely, bioburden determination study report and the most recent quarterly (b) (4) dose audit.

Please confirm receipt.

Sincerely,

Erik



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

Memorandum

Date: 09/01/11

EL 09/01/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: BLA STN 125359 (Erwinaze); Information Request

From: Laughner, Erik

Sent: Thursday, September 01, 2011 3:32 PM

To: 'Paul Plourde'

Subject: RE: Amendment 17

Hi Paul,

The letter of x-reference from (b) (4) in this recent amendment states that (b) (4) is the applicant of STN 125359. For the record, in your next submission, please provide a correct letter from (b) (4) authorizing EUSA Pharma as the holder of the BLA file.

Thanks,

Erik



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

Memorandum

Date: 08/26/11 ECL 08/26/11
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: BLA STN 125359 (Erwinaze); Advice/Information Request

From: Laughner, Erik
Sent: Friday, August 26, 2011 10:21 AM
To: Paul Plourde
Subject: RE: The use of (b) (4)

Good Morning Paul.

Please see the following response to your email:

Even if EUSA Pharma intends to use (b) (4) for one-time event, it should be included in section 3.2.P.3.1 Manufacturers of the BLA. (b) (4) is not listed in this section. In addition, you must provide process similarity (temperature the product is exposed to and duration is the main concern) of labeling packaging process at (b) (4).

Please confirm receipt.

Sincerely,

Erik

From: Paul Plourde [mailto:Paul.Plourde@eusapharma.com]
Sent: Friday, August 26, 2011 8:52 AM
To: Laughner, Erik
Subject: The use of (b) (4)

Erik

We wanted to make sure the Agency had clearly understood our submission SN 0014, dated April 21, 2011 to the BLA. This submission was made in response to a request for information from the Agency both formally, as a result of the PAI for (b) (4) (our packager/labeler), and informally, during the PAI of (b) (4).

This submission describes the details of the supply chain starting from (b) (4) to distribution sites in the US – the current (b) (4) and the proposed commercial site of (b) (4) (b) (4) In Section 2.1.5 (US Launch Packager/Labeler -- Transport to (b) (4) of this submission,

the Sponsor describes special plans for handling only the launch quantity of the product (b) (4) vial packs).

Since Erwinaze is a life-saving drug for children, EUSA is committed to having the commercial product ready to ship to sites quickly after approval. In the event the approval letter contains changes to the proposed label or Prescribing Information, the established supply chain in the UK would require a couple of weeks to develop and print new labels, package, and ship to the US. Therefore, EUSA is planning on labeling and packaging a small launch quantity at the (b) (4) clinical trials site in (b) (4) a -a onetime event. EUSA already uses this facility for labeling and packaging (b) (4). This launch quantity will provide Erwinaze to the market during the period our regular commercial supply chain gears up for commercial supply to the US.

The FDA response of August 4, 2011 to Question 18 (see below) in the CMC deficiency letter appears to indicate the FDA believes the use of (b) (4) is a permanent change in the supply chain.

“Shipping process consists of transport from (b) (4) (DP manufacture) to (b) (4) (labeling/packaging) to (b) (4) (distributor) to US distributor. . . . It appears that the labeling/packaging site will change to (b) (4). Please explain when this change will occur. . . .”

This is a one-time event using (b) (4) EUSA’s established supplier of labeling and packaging services for an approved drug, to ensure patients have drug available as soon as possible after approval.

Please call me if you have questions or want to discuss further. Could you confirm that the Agency understands the shipping process?

Paul

Paul V. Plourde, MD
Senior Vice President
Global Medical Oncology &
US Medical Affairs Head
EUSA Pharma
One Summit Square Suite 201
1717 Langhorne Newtown Road
Langhorne, PA 19047
Phone: 215 867-4923
Fax: 215 579-0384

(b) (6)



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

Memorandum

Date: 08/24/11 *SL 08/24/11*
From: Erik Laughner, RPM DBOP/ODP/CDER/FDA
Subject: EUSA Pharma (STN 125359/0); tcon regarding submission of CMC and clinical deficiencies and USAN review of proper name

DISCUSSION: Paul Plourde called to update FDA on the submission of the CMC information needed to resolve the pre-approval deficiencies. The first amendment which contained ~80% of the responses was targeted for week of August 29th. Two more amendments over the next month would follow to complete the responses.

With regard to the analysis of the archived clinical samples at (b) (4) EUSA Pharma anticipated providing the results and validations the week of September 5th.

Paul also updated FDA that USAN had begun the process of reviewing the two proposed Proper Names, (b) (4) USAN had committed to expediting the review and had sent out the ballots to the members for voting. Paul expressed concern that this particular issue not hold up any BLA approval if the CMC and clinical deficiencies had been satisfactorily addressed.



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

Memorandum

Date: 08/17/11 *ESL 08/17/11*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: BLA STN 125359 (Erwinaze); FDA review of EUSA Pharma 08/05/11 telecon minutes.

Background: A teleconference was held between FDA and EUSA Pharma on 08/05/11 to discuss numerous CMC deficiencies with the BLA. EUSA Pharma submitted their brief minutes via email and asked FDA to concur. The FDA CMC team reviewed the minutes and provided EUSA Pharma a slightly revised version for their record.



FDA 5 Aug 2011 FDA
reviewed.docx

From: Laughner, Erik
Sent: Wednesday, August 17, 2011 2:18 PM
To: 'Paul Plourde'
Subject: RE: TCON minutes

Paul,

The product and facility group reviewed your draft minutes as prepared. I inserted the FDA attendees and a few minor edits were made (not tracked). These attached minutes as provided by you and edited by FDA reflect the discussion accurately.

Erik

EUSA Pharma Draft Minutes

Meeting Date: August 5, 2011

Product: Erwinaze

IND/BLA: 290/125359

Subject: Clarification on draft responses/comments on CMC deficiencies

Participants:

FDA

Office of New Drugs

Office of Oncology Drug Products

Division of Biologic Oncology Drug Products

*Joseph Gootenberg	Deputy Division Director	*arrived later after initial introductions
Patricia Dinndorf	Clinical Reviewer	
Karen Jones	Chief Project Management Staff	
Norma Griffin (for Erik Laughner)	Regulatory Project Manager	
Gregory Reaman	Associate Office Director	

Office of Biotechnology Products

Division of Therapeutic Proteins

Barry Cherney	Deputy Division Director
Serge Beaucage	Product Quality Reviewer
Cristina Ausin	Product Quality Reviewer
Jacek Cieslak	Product Quality Reviewer
Nikolay Spiridonov	Product Quality Reviewer

Office of Compliance

Office of Manufacturing and Product Quality

Division of Good Manufacturing Practice Assessment

Patricia Hughes	Branch Chief (acting)
Kalavati Suvarna	Microbiology Product Quality Reviewer
Mary Farbman	Microbiology Product Quality Reviewer

EUSA

Tim Corn Chief Medical Officer

Paul Plourde

SVP and Global Erwinase Leader

Bill Bennett

VP of US Regulatory and QA



EUSA Consultant



Background

On July 11, 2011, the Sponsor received the Agency's CMC Deficiencies Memo. Responses from the Sponsor were submitted to the Agency on July 22, 2011 along with a meeting request. Follow-up responses were provided by the Agency on August 4, 2011 prior to the agreed August 5, 2011 meeting. EUSA Pharma (b) (4) found those follow up responses by the Agency to be very clear and helpful but requested the meeting occur as scheduled to gain clarification on one or two outstanding issues and to discuss the procedure for updating the BLA

These minutes reflect the conversation and agreements that were made. Once agreed, the full communication on the CMC deficiencies will be collated and submitted as part of the BLA.

Questions for Clarification

July 11, 2011 FDA O2: Your proposed DS release and stability acceptance criteria for specific activity is broader than your estimated manufacturing experience, based on the data submitted to the application. This acceptance criterion should ensure that you will consistently meet the expected quality attributes of the drug product. Please tighten this control to limits in line with any revision to the drug product specifications or provide a justification supported by data as to why this action is unnecessary.

July 22, 2011 EUSA Pharma Response: The specification originally proposed was (b) (4) U/mg. In line with the revised limits proposed for drug product (see Question 6 below), EUSA will tighten the release specification for specific activity for drug substance to (b) (4) U/mg'. This would encompass the release data available for DS batches, each of which has been processed on to drug product batches.

In addition, we will establish separate release and stability specifications, and tighten the stability specification to (b) (4)".

Does the Agency agree with these revisions?

August 4, 2011 FDA Response: Insufficient information was provided to evaluate the proposal. Understanding the process capability and defining limits based on a statistical analysis that provides some assurance that future lots will pass specification is a useful activity to assure manufacturability of the product. However, a statistical approach does not assess the potential impact to clinical performance at the allowable limits. Please include a justification for the proposed limits based on the impact to clinical performance and provide the data that support this assessment.

August 5, 2011 FDA T/C Clarification: The issues for Q2 and Q6 are the same. While we don't have any objection, *per se*, to your proposed limits, the justification for the specific activity specifications for DS and DP appears to be based principally on a statistical analysis of the consistency of the manufacturing process. Since the specific activity is a measure of the product purity, what we need you to do is relate the specification limits to the clinical experience, as you have done for the issue of deamidation, particularly with respect to the lower limit.

August 5, 2011 EUSA/HPA Response: We will provide a justification as to why the limits are acceptable based upon clinical performance in terms of product safety and efficacy.

July 11, 2011 FDA Q3: *The drug substance specification of "Comparable to ERS (Erwinaze Reference Standard)" for the peptide mapping method does not include objective criteria to assess what "comparable to reference standard" actually means. Objective criteria allow for consistent evaluation of product quality and should be established whenever the acceptance criteria are based on a comparison to a reference material. Please revise the acceptance criteria to include limits on the following: selected peak heights; peak areas; and peak retention times to ensure comparability to the ERS. In addition, limits on new peaks not observed in the ERS should be set based on a defined percentage of the total peak area.*

July 22, 2011 EUSA Pharma Response: We will revise the acceptance criteria for peptide mapping for drug substance as requested. In addition, and as requested in Question 12, we will include these same criteria in the peptide mapping release test for drug product.

Does the Agency agree with these revisions?

August 4, 2011 FDA Response: The proposed revisions are acceptable with the exception of the proposed acceptance criteria for new peaks in Unknowns, which are not present in ERS. A peak area of (b) (4) of the total peak area for each new peak is too high considering that these peaks results from the proteolytic fragmentation of a commensurately abundant species, the peptide fragments of which may or may not overlap with those of Erwinaze peptide fragments. A tighter control on the allowable peak area of new peaks other than those of the ERS is required to provide adequate assurance of the identity and purity of Erwinaze DS/DP. It may be acceptable to include an action limit that will initiate an investigation into the potential impact of a new impurity when observed in the peptide map.

August 5, 2011 FDA T/C Clarification: EUSA Pharma requested further clarification from the Agency regarding their response. The Agency stated that the need to improve the peptide map to eliminate overlaps and decrease the number of peaks had already been communicated. An impurities limit of (b) (4) or those impurities not part of the reference standard is acceptable but there is concern about the way new peaks will be handled. The Agency would like action limits established for new impurities detected at the limit of quantitation (typically 0.5% but sponsor must specify). The new impurities must be investigated as would any other deviation and the actual level in the batch will need to be determined (short and long chain peptides may give the same response at 220 but be present at significantly different weight concentration).

August 5, 2011 EUSA (b) (4) Response: A proposal for action limits for new peaks not present in the reference standard but present in Unknowns at $\geq 0.5\%$ total peak area will be submitted as part of the end-August submission package.

(b) (4)

July 22, 2011 EUSA Pharma Response: The specification originally proposed was ' (b) (4) U/mg'. We will tighten the drug product release and stability specification to (b) (4)' to reflect the manufacturing and clinical experience.

Does the Agency agree with this revision?

August 4, 2011 FDA Response: Insufficient information was provided to evaluate your proposal. Understanding the process capability and defining limits based on a statistical analysis that provides some assurance that future lots will meet specification is a useful activity to assure manufacturability of the product and a suitable shelf life. However, a statistical approach does not assess the potential impact to clinical performance at the allowable limits and inclusion of stability data beyond what would be expected to be representative of the clinical trial material is necessarily appropriate. Please include a justification for the proposed limits based on the impact to safety or efficacy and provide the data that support this assessment.

August 5, 2011 TCON: See Q2 for FDA clarification and EUSA/ (b) (4) response.

Addition items discussed at the teleconference:

Timelines

EUSA Pharma: Should outstanding items be supplied on a rolling basis or as 'bundles'?

FDA Response: Items should be supplied in as few 'bundles' as possible.

EUSA Pharma Response: Items will be supplied as three bundles: the majority of items by the end of August, a smaller bundle mid September and remaining items by end September (dates are included above against each question).

FDA Response: The proposal is acceptable

Media fills

FDA Question: When will the results of the most recent media fills be available?

EUSA Pharma Response: Results will be submitted at the end of September

Stability Data

FDA Comment: We would like to see an update of the stability data for the Drug Product, in particular, but also the Drug Substance if available. Your submission did not include two year data for all the batches and we would like to see the latest results.

EUSA Pharma Response: We will submit updates on the applicable stability studies by the end of August

Submission Organisation

FDA Comment: In your cover letter with the end August submission, we would like to see a comprehensive list of what's included in that submission and what will be included in the September submission to help us manage the responses properly. The September submission should have something similar.

EUSA Pharma Response: We will provide the requested indices with each Submission.

Monitoring Moisture Levels

FDA Comment: While we accept the submission of the lyophilizer validation data as a PMC (3Q 2012), until then you should monitor for moisture. Furthermore, we are concerned that you have not adequately defined the worst case locations for moisture in the lyophilizer. Absent validation, 4 vials per batch is not adequate for moisture monitoring. You should monitor at different locations and increase the number of vials tested for moisture per batch.

EUSA Pharma Response: We will submit a proposal for monitoring moisture levels at various locations in the lyophilizer as part of the end August package.

Shipping Validation

FDA Comment: We are concerned about the shipping validation. The validation submitted in the BLA was done with empty vials. For a validation, the vials should be filled with either water or buffer or some other simulant representing a filled vial. The validation should cover the worst case conditions for duration, temperature, load configuration etc. and should be performed with the commercial shipper. There should be adequate temperature monitoring throughout the load.

EUSA Pharma Response: We have understood your concerns and will submit a shipping validation protocol based on these issues by mid-September.



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

Memorandum

Date: 08/16/11

ESL 08/16/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: FDA Request for Information; BLA STN 125359 (Erwinaze); Response to EUSA Pharma information requests submitted on August 8, 2011 regarding a draft 163, and validation protocol and SOP for asparaginase activity assay. These 3 documents are attached at end of this memo for the record.

From: Laughner, Erik
Sent: Tuesday, August 16, 2011 9:30 AM
To: 'Paul Plourde'
Subject: STN 125359; FDA advice on draft 163 and validation protocol/sop for asparaginase assay
Importance: High

Paul,

Please see attached memo. Please confirm receipt.

Sincerely,

Erik



081611 FDA
Advice.doc (73 KB)

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

If you have received this message in error, do not use, disclose, reproduce, or distribute this message (including any attachments) and notify me immediately. Thank you.



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

Memorandum

Date: August 16, 2011
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: FDA Request for Information; BLA STN 125359 (Erwinaze); Response to EUSA Pharma information requests submitted on August 8, 2011 regarding a draft 163, and validation protocol and SOP for asparaginase activity assay.

In regard to your draft 163 submitted to FDA via email on August 8, 2011:

FDA has reviewed and agrees that the proposed method outline and reporting formats are reasonable. However, we request that the following information also be provided: a record or statement of the complete temperature history for the serum samples, including the records mentioned in sections 3.3.6, 3.2.2, and 3.3.3, or min/max records, in addition to the statements of continuous dry ice during shipping. If there were accidents or deviations in samples' storage and handling, or if spurious asparaginase values are encountered, please address these matters with fact-based reasoning.

In regard to your proposed (b)(4) validation protocol and SOP on the asparaginase activity assay submitted to FDA via email on August 8, 2011, we have the following comments:

1. Part 58 (GLP) and the 2001 Guidance on Bioanalytical Method Validation don't apply to this work, but we do not object to your using these references to outline validation and analysis plans, and to establish a quality model. We do not have a specific regulation or guidance to provide details for analytical conduct. We intend to authenticate records and assess fundamental data integrity, in evaluating your measurements of a surrogate endpoint to an efficacy study.
2. We acknowledge that the reagents/reactants, and the calibrators /quality control sample concentrations are approximately the same as the reference studies, so we expect the results to be comparable to the work of Asselin *et al.* and others.
3. We recommend avoiding plasticware and water treated with diethylpyrocarbonate (DEPC), a known inhibitor of asparaginase [Bagert-U and Roehm-KH, BBA 999:36-41, 1989] and mitochondrial MDH [Anderton-BH and Rabin-BR, Eur J. Biochem. 15:568-573, 1970].

4. In regard to the validation protocol for the quantitation of the enzymatic activity of L-Asparaginase in human serum, the validation parameters for selectivity, precision, accuracy, limits of quantitation, linearity, and stability were evaluated and the following limits were proposed:
- a. The RSDs for intra-assay precision and accuracy of the calibration curve in terms of L-asparaginase concentrations should be $\leq 20\%$ to $\leq 25\%$ and $\leq 25\%$ to $\leq 30\%$, respectively.
 - b. The RSDs for inter-assay precision and accuracy of the calibration curve in terms of L-asparaginase concentrations should be $\leq 20\%$ to $\leq 25\%$ and $\leq 25\%$ to $\leq 30\%$, respectively.
 - c. The RSDs for intra-assay precision and accuracy of QC L-asparaginase samples over the range of concentration tested should be $\leq 20\%$ to $\leq 25\%$.
 - d. The RSDs for intra-assay precision and accuracy of QC L-asparaginase samples over the range of concentration tested should be $\leq 20\%$ to $\leq 25\%$.
 - e. The % RSD for precision at ULOQ and LLOQ should be $\pm 20\%$ and $\pm 25\%$, respectively. The % RSD for accuracy at ULOQ and LLOQ should be $\pm 20\%$ and $\pm 25\%$, respectively.
 - f. The acceptance criterion for the short term stability of *E.coli* L-Asparaginase and Erwinase at 2-8°C for 24 hr is that the average (mean) values for the activities at each of QC concentration tested should be within $\pm 25\%$ of their respective nominal values.
 - g. The proposed acceptance criterion for freeze-thaw stability of *E.coli* L-Asparaginase and Erwinase is that the average (mean) values for the activities at each of QC concentration tested should be within $\pm 25\%$ of their respective nominal values.

The proposed limits for all the above parameters appears excessively broad given that these limits allow the determination of L-asparaginase activity values in human plasma to differ by 50% at the extremes of these limits. Please tighten these limits based on the analytical capabilities of the assay or provide a justification, supported by data, demonstrating that these limits are acceptable for each validation parameter.

5. You have proposed to determine L-Asparaginase V_{max} in the samples by fitting the data to a 4-parameter equation using the parameters derived from the fit of the standard curve. However, enzyme kinetic assays are typically carried out by measuring the product at an initial rate that is still linear. While it is possible to measure the complete reaction curve and fit this data to a non linear rate equation, we are not sure that this approach using a complex sample as human

serum is the optimal approach. Please provide a justification why this is the optimal approach.

6. The validation protocol does not provide for evaluation of the assay robustness to variability in pH, reaction temperature, and volume/activity of critical reagents, such as asparaginase standards and enzyme/substrate mix. Please consider including these parameters in your validation protocol to better assess the robustness of the assay. Please also provide a description of the procedures and criteria used for the qualification of new batches of critical reagents that are required for performing the assay.

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



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

Memorandum

Date: August 5, 2011
From: Norma Griffin; Regulatory Project Manager, DBOP/OODP/OND/CDER/FDA *NG*
Subject: Draft Responses / Comments - BLA 125359 EUSA Pharma and "Erwinaze" Meeting of August 5, 2011 to Discuss CMC Deficiencies *8/5/2011*

Meeting Type: Teleconference
Meeting Category: Other - teleconference
Meeting Date and Time: August 5, 2011; 11:00 AM to 12:00 PM (ET)
Meeting Location: White Oak Building 22; Conference Room 3201
IND Number: BLA 125359
Product Name: Erwinaze
Sponsor Name: EUSA Pharma
Meeting Requestor: Paul Plourde - Senior Vice President, Global Medical Oncology & US Medical Affairs Head
Meeting Chair: Barry Cherney
Meeting Recorder: Norma Griffin (for Erik Laughner)

LIST OF FDA ATTENDEES:

Office of New Drugs
Office of Oncology Drug Products
Division of Biologic Oncology Drug Products

Joseph Gootenberg Deputy Division Director
Patricia Dinndorf Clinical Reviewer
Karen Jones Chief Project Management Staff
Norma Griffin (for Erik Laughner) Regulatory Project Manager
Gregory Reaman Associate Office Director

Office of Biotechnology Products
Division of Therapeutic Proteins

Barry Cherney Deputy Division Director
Serge Beaucage Product Quality Reviewer
Cristina Ausin Product Quality Reviewer
Jacek Cieslak Product Quality Reviewer
Nikolay Spiridonov Product Quality Reviewer

DRAFT

DRAFT

DRAFT

BLA 125359 – Erwinaze
TCON of August 5, 2011 with EUSA Pharma

Office of Compliance
Office of Manufacturing and Product Quality
Division of Good Manufacturing Practice Assessment
Biotech Manufacturing Assessment Branch

Patricia Hughes

Kalavati Suvarna

Mary Farbman

Branch Chief BMAB

Microbiology Product Quality Reviewer

Microbiology Product Quality Reviewer

LIST OF SPONSOR ATTENDEES:

EUSA

Tim Corn

Paul Plourde

Bill Bennett

Chief Medical Officer

Senior Vice President; clinical

Vice President of US Regulatory and QA

(b) (4)

Consultant

(b) (4)

Meeting Purpose: The purpose of this meeting is to discuss the deficiencies identified in the tertiary review from both DTP and BMAB for the Erwinaze BLA.

These preliminary responses to CMC issues were sent to EUSA Pharma on August 4, 2011.

BLA 125359 – Erwinaze
TCON of August 5, 2011 with EUSA Pharma

Product

In regard to Erwinaze drug substance (DS) manufacturing process and process controls:

Q2: Your proposed DS release and stability acceptance criteria for specific activity is broader than your estimated manufacturing experience, based on the data submitted to the application. This acceptance criterion should ensure that you will consistently meet the expected quality attributes of the drug product. Please tighten this control to limits in line with any revision to the drug product specifications or provide a justification supported by data as to why this action is unnecessary.

EUSA Pharma: The specification originally proposed was (b) (4). In line with the revised limits proposed for drug product (see Question 6 below), EUSA will tighten the release specification for specific activity for drug substance to (b) (4). This would encompass the release data available for DS batches, each of which has been processed on to drug product batches.

In addition, we will establish separate release and stability specifications, and tighten the stability specification to (b) (4).

Does the Agency agree with these revisions?

FDA Response: Insufficient information was provided to evaluate the proposal. Understanding the process capability and defining limits based on a statistical analysis that provides some assurance that future lots will pass specification is a useful activity to assure manufacturability of the product. However, a statistical approach does not assess the potential impact to clinical performance at the allowable limits. Please include a justification for the proposed limits based on the impact to clinical performance and provide the data that support this assessment.

Discussion During 8/5/2011 Teleconference: Because the issues for Question 2 (Q2) and Question 6 (Q6) are similar, the discussion during the teleconference was for both Q2 and Q6.

Specific activity is a measure of product purity. Because the specific activity specifications for drug substance and drug product were based on statistical analysis of the manufacturing process data, FDA asked that EUSA Pharma provide justification for the proposed limits (particularly at the lower end of the limits) based on the impact the proposed specifications may have on the clinical performance of the product. EUSA Pharma agreed to provide justification for the proposed specification limits based on clinical study data.

Q3: The drug substance specification of “Comparable to ERS (Erwinaze Reference Standard)” for the peptide mapping method does not include objective criteria to assess what “comparable to reference standard” actually means. Objective criteria allow for consistent

BLA 125359 – Erwinaze
TCON of August 5, 2011 with EUSA Pharma

evaluation of product quality and should be established whenever the acceptance criteria are based on a comparison to a reference material. Please revise the acceptance criteria to include limits on the following: selected peak heights; peak areas; and peak retention times to ensure comparability to the ERS. In addition, limits on new peaks not observed in the ERS should be set based on a defined percentage of the total peak area.

EUSA Pharma: We will revise the acceptance criteria for peptide mapping for drug substance as requested. In addition, and as requested in Question 12, we will include these same criteria in the peptide mapping release test for drug product.

Does the Agency agree with these revisions?

FDA Response: The proposed revisions are acceptable with the exception of the proposed acceptance criteria for new peaks in Unknowns, which are not present in ERS. A peak area of (b) (4) of the total peak area for each new peak is too high considering that these peaks result from the proteolytic fragmentation of a commensurately abundant species, the peptide fragments of which may or may not overlap with those of Erwinaze peptide fragments. A tighter control on the allowable peak area of new peaks other than those of the ERS is required to provide adequate assurance of the identity and purity of Erwinaze DS/DP. It may be acceptable to include an action limit that will initiate an investigation into the potential impact of a new impurity when observed in the peptide map.

Discussion During 8/5/2011 Teleconference: FDA reiterated the need for improved peptide mapping and explained that their concern is for the identification of new peaks in 'Unknowns' that are not present in the reference standard. FDA requested that EUSA Pharma establish an action limit for new impurities (typically near the limit of quantitation), and investigate and characterize any newly identified impurities. FDA also recommended that their response should include discussion on the sensitivity of the assay relative to the actual amount of an impurity and not simply as a percent of the total peak area. EUSA Pharma agreed to submit proposed action limits in their submission package due at the end of August 2011.

Q4: Regarding your validation of impurity removal: the general approach you have taken was to obtain in-process samples at different manufacturing stages (e.g., bulk extract, CM-6 chromatography pool and Bulk DS) during the manufacture of the three process validation batches, and then determine the level of impurities in these materials. The data from these analyses show that the purification process has adequately removed the various impurities evaluated. For example, you have shown that Erwinia (b) (4) are cleared to levels below the detection limit of the assay in bulk DS. However, validation batches are manufactured to the target operating parameters and provide little information on product quality when the process is operated at the allowable extremes of these parameters or when there is considerable variability in the input impurity load (e.g., host cell protein or DNA). In these situations, assessment of the capacity of the manufacturing process to clear

BLA 125359 – Erwinaze
 TCON of August 5, 2011 with EUSA Pharma

impurities at the allowable extremes of the in-process parameters plays an important role in evaluating the robustness of a purification process for clearing process related impurities. This is viewed as an integral component in validating impurity clearance and eliminating routine testing for that impurity at release. In some cases, a demonstration that the process has excess clearance capacity (i.e., through the use of laboratory spiking studies) may be used in lieu of worst case studies. Please include impurity testing in the release specifications or provide additional data supporting, with a high degree of confidence based on robustness testing, that the process will clear the impurities. Impurities include

(b) (4)

EUSA Pharma: We will include tests for (b) (4) in the release specification for drug substance. We will include testing for (b) (4) in the release specification for drug product (b) (4)

Does the Agency agree with this approach?

FDA Response: Specification limits for the above impurities should be established on the basis of the purification process capability and on the historical test results for these impurities along with an understanding of the potential impact to clinical performance. The proposed specification limits for (b) (4) than the actual test results for the impurities. These limits are not representative of the capability of the purification process and not in line with clinical experience; the proposed specification limits for (b) (4) (b) (4) should therefore be tightened.

Discussion During 8/5/2011 Teleconference: EUSA Pharma acknowledged and agreed with FDA's response. There was no discussion during the meeting.

Regarding the Erwinaze drug product (DP) manufacturing process and process controls:

Q5: Concerning the IEX-HPLC test method

- a. This method shows multiple product related substances/impurities, including various (b) (4). While you established acceptance criteria for the main peak and the sum of all (b) (4), this control strategy may not provide an adequate assessment of product quality because each product related variant may pose a different risk to product quality. In such cases, individual, and not collective acceptance criteria, should be established. For example, all (b) (4) do not impact product potency to the same

BLA 125359 – Erwinaze
 TCON of August 5, 2011 with EUSA Pharma

extent. Those sites that alter potency should be more tightly controlled than other sites. With this in mind, please identify the exact nature of the variant in each peak, discuss the specific risks to product quality and revise the specification to ensure adequate control of these risks.

EUSA Pharma: EUSA will revise the release specification for the IE-HPLC method to include action limits for each individual (b) (4) peak (described below), in addition to the overall specification of (b) (4) for the sum of all (b) (4) species. We believe this will ensure adequate control of the risks. Available information on the nature of the variants plus the risks to product quality based on clinical experience and potency assessment are discussed below, with additional supporting information in the Appendix.

Does the Agency agree with this approach?

FDA Response: Yes. As each (b) (4) variant has a similar impact to product potency, establishing action limits rather than a specification will provide sufficient assurance that the risk to product quality will be evaluated. Given the low standard deviation in the measurement of IE-HPLC peak areas, the proposed action limits for peaks C, D and E provide adequate control on the levels of (b) (4) present in the product at release.

Discussion During 8/5/2011 Teleconference: EUSA Pharma acknowledged and agreed with FDA's response. There was no discussion during the meeting.

- b. *You have established the stability specification for designated species at (b) (4) presumably based on the observation that the levels of (b) (4) product in the clinical lots reached (b) (4) two to three years after release and that potency did not appear to be affected. However, (b) (4) product also may be associated with an enhanced immune response. While it is reasonable to suggest that clinical experience included material that may have contained (b) (4) (b) (4) species, your specification would allow for levels significantly more than clinical experience would support. Please revise the stability specification to better reflect clinical experience or provide a justification as to why the proposed limit is acceptable.*

EUSA Pharma: There is clinical experience with lots used during the pivotal trial and the treatment IND that supports a stability specification of (b) (4). The will revise the proposed specification of (b) (4)% to more accurately reflect the clinical experience. We will also commit to monitor and review the stability data from the individual (b) (4) to assess the need for potential alert limits on designated species.

BLA 125359 – Erwinaze
TCON of August 5, 2011 with EUSA Pharma

Does the Agency agree with this revision to the stability specification and the commitment to monitor individual peaks on stability?

FDA Response: The revised DP stability specification of (b) (4) for the (b) (4) is acceptable given its correlation with the content of the same (b) (4) species in the clinical trial lots CAMR134 and CAMR135. The commitment to monitor individual (b) (4) Erwinase DP species during annual stability assessment is also acceptable.

Discussion During 8/5/2011 Teleconference: EUSA Pharma acknowledged and agreed with FDA's response. There was no discussion during the meeting.

Q6: The specific activity determinations used for release and stability showed that the results for the commercial and clinical trial material are very similar and ranged between (b) (4). Furthermore, the lowest and highest specific activity values reported for this test were (b) (4), respectively. However, the proposed specification of (b) (4) for specific activity is much broader than your manufacturing history and the clinical experience submitted to the application. Because the specific activity measurement evaluates the relative amounts of active ingredient to product and process related impurities, we view this parameter as an important control measure for product purity. Please revise the acceptance criterion for the test results of this assay to better reflect your clinical and manufacturing experience and provide the supporting data along with your rationale for the approach taken.

EUSA Pharma: The specification originally proposed was (b) (4). We will tighten the drug product release and stability specification to (b) (4) to reflect the manufacturing and clinical experience.

Does the Agency agree with this revision?

FDA Response: Insufficient information was provided to evaluate your proposal. Understanding the process capability and defining limits based on a statistical analysis that provides some assurance that future lots will meet specification is a useful activity to assure manufacturability of the product and a suitable shelf life. However, a statistical approach does not assess the potential impact to clinical performance at the allowable limits and inclusion of stability data beyond what would be expected to be representative of the clinical trial material is necessarily appropriate. Please include a justification for the proposed limits based on the impact to safety or efficacy and provide the data that support this assessment.

BLA 125359 – Erwinaze
TCON of August 5, 2011 with EUSA Pharma

Discussion During 8/5/2011 Teleconference: Because the issues for Question 2 (Q2) and Question 6 (Q6) are similar, the discussion during the teleconference was for both Q2 and Q6. See summary recorded in ‘Discussion During 8/5/2011 Teleconference’ for Question 2.

Q7: You have indicated that SDS-PAGE is used as a qualitative procedure for identification of Erwinaze DP but will not be used as a stability-indicating test because the purity of the DP on stability will be assessed using SE-HPLC, RP-UPLC, and IEX-HPLC. However the SDS-PAGE method provides information on product truncations for which the above listed methods have not been validated. Therefore, SDS-PAGE should be used as a DP stability-indicating test method. Furthermore, the SDS PAGE results at release and stability should have defined objective criteria regarding what constitutes “Comparable to Erwinaze Reference Standard”. Please revise your drug product release and stability specifications to include SDS PAGE analysis and well defined objective criteria for acceptable results.

EUSA Pharma: We will include SDS-PAGE in the revised stability protocol which we will submit in a revision to the BLA.

In addition, and in line with our criteria for SDS-PAGE analysis of drug substance, we will introduce defined objective criteria regarding what constitutes “Comparable to Erwinaze Reference Standard” for SDS-PAGE.

FDA Response: Although the proposal may be acceptable as an interim measure, FDA believes that the assay should be optimized so that it can reliably detect impurities that are present at ≥ 1.0 % in your drug product. Please describe the assay sensitivity relative to what is administered to patients rather than as a percent of the protein loaded and, if necessary, provide a post marketing commitment to increase assay sensitivity.

Discussion During 8/5/2011 Teleconference: EUSA Pharma acknowledged and agreed with FDA’s response. There was no discussion during the meeting.

Q8: The use of orthogonal test methods for assessing a critical quality attribute of the DP may be used to validate the sensitivity, precision and accuracy of the test method used for routinely monitoring this attribute. Although you showed that size exclusion (SE) HPLC and analytical ultracentrifugation (AUC) as orthogonal test methods provided similar results at release, data indicating that little or no aggregates are detected at release by either method is not informative regarding the suitability of the SE-HPLC method for accurate quantitation of aggregates during storage. Please submit data indicating that the SE-HPLC analysis provides meaningful results regarding aggregate content by performing a direct comparison between the SE-HPLC and Sedimentation Velocity-AUC tests, in a side-by-side fashion. We recommend that this comparison be performed under multiple stress conditions that are known to induce aggregates. However, other studies may be acceptable.

DRAFT

DRAFT

DRAFT

BLA 125359 – Erwinaze
TCON of August 5, 2011 with EUSA Pharma

EUSA Pharma: We will conduct side-by-side studies to directly compare the levels of aggregates seen by SE-HPLC and Sedimentation Velocity-AUC tests, and will submit the data to the Agency by the end of September 2011.

FDA Response: The proposal is acceptable.

Discussion During 8/5/2011 Teleconference: EUSA Pharma acknowledged and agreed with FDA's response. There was no discussion during the meeting.

Q9: You are proposing a qualification protocol for your drug product reference standard that includes assays used for release testing and additional characterization assays. In general, the acceptance criteria you have established for the analytical results of the qualification program are based on a calculation of the mean \pm 3SD and would allow for product characteristics in the new reference standard that are out of trend with the desired or expected product characteristics. In our view, the reference standard chosen should be suitable for its intended purpose and provide assurance that the critical quality characteristics of the product do not drift over time. This is particularly important when results of an analytical method are expressed as a percentage of the reference standard. In such cases, the product attribute of the new standard must be determined to be highly similar, quantitatively, to the previous standard with a high degree of confidence. Please revise your reference standard qualification program by tightening your acceptance criteria for attributes that are relevant to the intended purpose of the standard and where appropriate, provide a statistical analysis that describes the 95% confidence interval. Please include your rationale for the approaches taken in the proposed protocol. Please note that additional sampling beyond what is typically used in release testing may be required to increase assay precision. Alternatively, you may withdraw your proposed protocol from the BLA and submit a revised one as a post-approval supplement.

EUSA Pharma: We accept the observation, and will withdraw the reference standard qualification protocol from the BLA and will submit a revision as a post-approval supplement, taking into account the Agency's comments by November 2011.

FDA Response: The proposal is acceptable. It may be useful to know that FDA is co-sponsoring a meeting with the International Alliance for Biological Standardization (IABS) entitled "Reference Standard for Therapeutic Proteins: Their Relevance, Development, Qualification and Replacement" to be held on September 20-21, 2011. This meeting may be helpful in developing a suitable qualification protocol.

Discussion During 8/5/2011 Teleconference: EUSA Pharma acknowledged and agreed with FDA's response. There was no discussion during the meeting.

DRAFT

DRAFT

DRAFT

BLA 125359 – Erwinaze
TCON of August 5, 2011 with EUSA Pharma

Q10: Your proposed post-approval stability program includes a container closure integrity (CCI) test that has not been validated. In order to ensure that the product remains sterile throughout its shelf life, please include sterility testing at relevant time points in your post-approval stability protocol until the CCI test is validated and submit a revised DP stability protocol.

EUSA Pharma: We will include sterility testing at the relevant time points on stability until such time as the proposed CCI test has been validated, and will update and submit a revised drug product stability protocol to reflect this by end of August 2011

When the CCI test has been validated we will submit the data for the validation as part of a CBE30 request to remove sterility testing from the stability test protocol.

FDA Response: The proposal is acceptable.

Discussion During 8/5/2011 Teleconference: EUSA Pharma acknowledged and agreed with FDA's response. There was no discussion during the meeting.

Q11: We have noted that measurements of K_m and k_{cat} are not included in the stability protocol for Erwinaze DP. As these enzyme characteristics provide more robust information on the enzymatic activity of this product than your activity assay, conducted at a single substrate concentration, please add K_m/k_{cat} measurements, with acceptable acceptance criteria, to the stability protocol for Erwinaze DP or provide a justification as to why this is unnecessary

EUSA Pharma: We will include K_m and k_{cat} in the drug product (DP) stability protocol as requested if required. However, we would like to present the following information on K_m and k_{cat} as evaluated in the forced degradation program which was undertaken.

Can the Agency advise if K_m and k_{cat} should be included in the stability protocol for Drug Product?

FDA Response: Although the experimental data provided is consistent with the hypothesis that these additional measurements may not be useful, insufficient information has been provided to reach a definitive conclusion. Until such data is obtained, FDA recommends including measurement of K_m and k_{cat} for DP in the stability testing program.

Regarding the experimental data submitted:

- a. Many of the stress conditions employed did not result in loss of product potency and therefore the ability of these assays to detect changes in potency for a specific degradation pathway is unclear. FDA would recommend using stress conditions that cause an incremental loss of product potency in your activity assay when doing these

BLA 125359 – Erwinaze
TCON of August 5, 2011 with EUSA Pharma

comparisons but recognize that certain conditions may not be stability-indicating for potency. Such studies may indicate that a measure of enzyme kinetics using a non natural substrate is not useful.

- b. The lack of changes in K_m and k_{cat} values may reflect the lack of affinity of your non-natural substrate for the enzyme, thereby resulting in a decreased ability for detecting subtle changes in the structure/conformation of Erwinaze. A more physiologically relevant substrate should be used when developing a sensitive measure of enzyme kinetics and evaluating this assay's suitability as a stability-indicating assay. Please consider developing a better assay for K_m and k_{cat} measurements as discussed in Q19.

Discussion During 8/5/2011 Teleconference: EUSA Pharma acknowledged and agreed with FDA's response. There was no discussion during the meeting.

Q12: We noted that your list of release tests for Erwinaze DP does not include a specific identity test that provides a definitive assessment of the product's identity. Although you have multiple methods, which in combination provide some assurance of identity, given the constantly changing manufacturing landscape and the presence of similar products on the market, we strongly recommend the use of definitive identity test of the drug product (e.g. peptide mapping, western blot or mass spectrometry). Please include a definitive identity test for release of Erwinaze DP or a justification as to why this is unnecessary.

EUSA Pharma: We will introduce peptide mapping as an identity test for commercial DP at release.

We can confirm that peptide mapping has been validated as an identity test for DP and we have compiled a comprehensive release data set for DP batches CAMR 144 – 150.

Can the Agency confirm this approach is acceptable?

FDA Response: This approach is acceptable pending resolution of the issue associated with the tighter control on the allowable peak area for new peaks other than those of the ERS, as delineated in the Agency's comment to your response to Question 3.

Discussion During 8/5/2011 Teleconference: EUSA Pharma acknowledged and agreed with FDA's response. There was no discussion during the meeting.

Q13:



BLA 125359 – Erwinaze
 TCON of August 5, 2011 with EUSA Pharma

(b) (4) A held a discussion on this subject with Dr Anastasia Lolos, lead FDA Inspector during the pre approval inspection (PAI). Dr. Lolos advised (b) (4) that the (b) (4) (b) (4) (b) (4) could not be considered in this review cycle as there was no data to support its inclusion. Therefore, it was agreed that the best way forward was to remove the proposed (b) (4) and continue to use the (b) (4) assembly as used for the conformance batches until such time as data is generated for a (b) (4) (b) (4) (b) (4). (b) (4) confirms that it has taken this course of action and that the media fills performed since the PAI have utilized the same filtration assembly as used for the conformance batches.

EUSA Pharma: Does the Agency concur with this approach?

FDA Response: This response is adequate. The information should be submitted as an amendment to the BLA.

Discussion During 8/5/2011 Teleconference: EUSA Pharma acknowledged and agreed with FDA's response. There was no discussion during the meeting.

Q14: Revise the (b) (4) hold time for the step (b) (4) in drug product manufacturing. The revised hold time should be supported by bioburden data at scale.

EUSA Pharma: We will revise the (b) (4) hold time (b) (4) (b) (4) to a maximum (b) (4).

We believe that this data adequately supports the (b) (4) time, does the Agency concur?

FDA Response: This response is adequate. The information should be submitted as an amendment to the BLA.

Discussion During 8/5/2011 Teleconference: EUSA Pharma acknowledged and agreed with FDA's response. There was no discussion during the meeting.

Q15: Submit a revised container-closure integrity study for the Erwinaze drug product. The following items should be included in the revised validation study:

- a. Determination of the sensitivity of the method
- b. Use of a bacterial challenge concentration of $> 1 \times 10^6$ CFU/mL
- c. Re-qualification of the crimping machine with media filled vials

BLA 125359 – Erwinaze
TCON of August 5, 2011 with EUSA Pharma

A draft protocol addressing each of the above items was provided to FDA in BLA Amendment # 15 on the 27th April 2011. A copy of the protocol is also attached to this response. Execution of this protocol and submission of the data to the Agency is expected to be completed at the end of December 2011.

Can the Agency confirm that the submitted protocol was acceptable? Can the Agency also confirm that the submission of the data from this study is as a post-approval commitment as indicted by the Agency in question number 23 below.

FDA Response: The dye ingress CCIT study for the stability program will be validated with a lactose simulant instead of product. If there is any interference of product with absorbance measurement, it should be evaluated during validation of the test method. Otherwise, the response is adequate.

Discussion During 8/5/2011 Teleconference: EUSA Pharma acknowledged and agreed with FDA's response. There was no discussion during the meeting.

Q16: Submit performance qualification data for the Erwinaze lyophilization process. The data should support the following:

- a. *The proposed lyophilization cycle and product load configurations*

EUSA Pharma: (b) (4) will perform lyophilization cycle PQ on the load configuration that is currently used in the manufacturing process. This will include the qualification of the critical quality attributes (cake and reconstituted solution appearance, reconstitution time, leakage) as described in the freeze dryer characterization strategy document (PPC-41-01-STR-01) previously submitted to the Agency. This work will also include moisture and temperature mapping of the loaded chamber. Details of how and when these studies will be conducted are proposed below.

- b. *Temperature uniformity in the chamber when loaded*

EUSA Pharma: Full temperature mapping within shelves and across the chamber will be performed on the normal, maximum, load and a theoretical, minimum, load configuration. Because of the risk that would be posed to product by introducing

(b) (4)
(b) (4) in place of Erwinase. It is anticipated that that this work will commence in Sept 2011 (during the next facility shutdown) and will be completed with data available by the end of November 2011.

BLA 125359 – Erwinaze
TCON of August 5, 2011 with EUSA Pharma

- c. *Accuracy of filling and stoppering and their impact on Erwinaze drug product lyophilization*

EUSA Pharma:

(b) (4)

(b) (4)

(b) (4)

- d. *Identification of worst chamber/shelf locations with regard to moisture*

Historical data for moisture content over the last 16 batches previously submitted to FDA (reference: Strategy for the Process Characterization of the Freeze Dryer, PPC-41-01-STR-01) demonstrates that moisture is controlled well within the final product specification (b) (4). The specification for moisture content has also subsequently been tightened to (b) (4). However, (b) (4) will provide PQ data to identify worst case chamber and shelf locations for vial moisture content. (b) (4) proposes to perform this using the normal (maximum) load configuration during the manufacture of batches commencing in Sept 11 (batch CAMR 151) and completion by end of March 2012 (batch CAMR 153).

DRAFT

DRAFT

DRAFT

BLA 125359 – Erwinaze
TCON of August 5, 2011 with EUSA Pharma

In the event there is a requirement to process a part load during routine production, (b) (4) proposes that it would qualify moisture distribution concurrently and submit the data to the agency for approval.

Completion of the above activities is dependent upon our manufacturing campaign schedule. Consequently temperature mapping data will not be available until completion of the facility shutdown at the end of Nov 2011. Moreover, moisture mapping data will not be available until the completion of the manufacturing campaign for the next three batches (CAMR 151-153) in March 2012. (b) (4) therefore requests the agency considers accepting completion of this work as a post approval commitment if in agreement with the approach outlined.

Does the Agency concur with this approach?

FDA Response: With respect to the temperature mapping study, please explain how (b) (4) is same as the placebo for Erwinaze drug product and how data from this simulant would be supportive of Erwinaze lyophilization process.

The performance qualification runs report should provide details of the load configurations (vials per shelf), process parameters controlled during lyophilization such as shelf temperature, condenser temperature and chamber pressure. Placebo with seeded product vials can be used for the PQ runs. The details of parameters monitored during the PQ runs such as product temperature (obtained from thermocouples inside vials), actual chamber pressure, and the pressure readout (measures partial pressure of water vapor, an indicator of moisture in the chamber) should be included. The moisture content of the vials from worst case locations should be assessed. The fill weight and stopper inspection data should be included for the PQ runs.

The lyophilization PQ information and data can be submitted as a post-marketing commitment. However, moisture content in vials from different locations of the lyophilizers should be monitored until the lyophilization process is validated. The locations and number of vials tested should be specified.

Discussion During 8/5/2011 Teleconference: EUSA Pharma acknowledged and agreed with FDA's response. There was no discussion during the meeting.

*Q17: Provide validation data for the (b) (4)
Alternatively, provide a letter of authorization to the applicable (b) (4) Master File.*

EUSA Pharma: A letter of authorization to the applicable (b) (4) Master File will be submitted to the Agency.

DRAFT

DRAFT

DRAFT

BLA 125359 – Erwinaze
TCON of August 5, 2011 with EUSA Pharma

FDA Response: There are no timelines when the letter of authorization to the applicable (b) (4) Master File will be submitted. The letter of authorization should indicate where the validation data and information for the (b) (4) are located. Submission of an electronic document containing the validation data from the Master file would help with timely review of the BLA.

Discussion During 8/5/2011 Teleconference: EUSA Pharma acknowledged and agreed with FDA's response. There was no discussion during the meeting.

Q18: Provide validation protocol for shipping Erwinaze drug product from (b) (4) the US market to support transport conditions and configurations.

EUSA Pharma: A formal shipping validation protocol covering transport conditions from (b) (4) the US will be submitted by 16th September 2011.

To provide an immediate and conclusive answer to the Division's questions about the impact of the packaging and labeling operations at (b) (4) and of transport to the US, a formal comparative ICH stability study of packaged 147B110 from the US was initiated in May 2011.

This study will evaluate the real time manipulations of storage, processing and transport to demonstrate that there is no adverse effect on the quality, identity, purity and strength of Erwinaze® products over the shelf life of the product, as compared with the bulk vial lot, CAMR 147, which is also on stability. Lot 147B110 was chosen since it experienced a number of events of concern to the FDA inspector of (b) (4) (the packager) -- moving in and out of cold storage more than once during packaging and a small temperature excursion (to 14.5 °C) during transport from (b) (4).

Beginning in September 2010, about (b) (4) vial packs of this Drug Product lot were imported into the US and this lot is currently in clinical distribution. A portion of this lot was transported back to (b) (4) and put on a comparative stability study. The study plan and the approved stability protocol were submitted to the BLA as SN 0014, dated April 21, 2011 as requested by the (b) (4) Inspector.

Data from the initial pull and the comparative data from the ongoing CAMR 147 stability study are presented below. The 15 Month data from the packaged lot shipped back to (b) (4) (b) (4) for stability testing show results comparable to those from the bulk vial lot that did not enter the supply chain. Since this stability aliquot of 147B110 actually experienced two trans-Atlantic flights followed by customs clearance and truck transport, it is considered a worst-case study. Therefore, although it represents only a single shipment, it is more compelling than a typical simulated shipment validation.

DRAFT

DRAFT

DRAFT

BLA 125359 – Erwinaze
TCON of August 5, 2011 with EUSA Pharma

Does the Agency accept this study as a fulfillment of the requirements for shipping validation?

FDA Response: Shipping process consists of transport from (b) (4) (DP manufacture) to (b) (4) (b) (4) (labeling/packaging) to (b) (4) (distributor) to US distributor. The stability testing from one lot does not validate the shipping process itself. It appears that the labeling/packaging site will change to (b) (4) Please explain when this change will occur. A shipping validation protocol to address commercial shipping process should be submitted to the BLA.

Discussion During 8/5/2011 Teleconference: EUSA Pharma acknowledged and agreed with FDA's response. There was no discussion during the meeting.

DRAFT

DRAFT

DRAFT

BLA 125359 – Erwinaze
TCON of August 5, 2011 with EUSA Pharma

(b) (4)

Does the Agency agree with this approach?

FDA Response: FDA agrees with the approach to conduct a more formal risk assessment (i.e. per ICH Q9) that utilizes quantitative metrics for potential severity, detectability, and likelihood of (b) (4)s and submit this report by the end of August 2011 as a post marketing commitment. FDA also agrees that extractable data derived from the respective suppliers can be used to support your risk assessment. In the event that the suppliers are unable to support this request or a risk is identified, FDA believes that appropriate studies should be performed to ensure that the risk to product quality is appropriately mitigated.

Discussion During 8/5/2011 Teleconference: EUSA Pharma acknowledged and agreed with FDA's response. There was no discussion during the meeting.

Q19: Measurements of enzyme kinetic parameters (K_m and k_{cat}) using a physiologically relevant substrate are likely to provide valuable information on the subtle enzyme conformational changes that may affect product potency. We noted that you employed L-aspartic acid β -hydroxamate, instead of the physiological substrate, L-Asparagine, for release testing of Erwinaze DS/DP. The affinity of Erwinaze for L-Asparagine is ~ 10-fold better than for L-aspartic acid β -hydroxamate. Thus, the use of this lower affinity substrate for Erwinaze may lead to a lack of sensitivity in detecting meaningful changes in the conformation of Erwinaze, which may have a negative effect on its in vivo potency. Please submit your plan for revising the enzyme kinetic assay to include L-Asparagine as

DRAFT

DRAFT

DRAFT

BLA 125359 – Erwinaze
TCON of August 5, 2011 with EUSA Pharma

the substrate when measuring K_m and k_{cat} for DS and DP at release or provide data supporting the use of L-Aspartic acid β -hydroxamate, instead of L-Asparaginase, as a substrate.

EUSA Pharma: EUSA will commit to building on the enabling work (described below) by finalizing a prototype assay for K_m and k_{cat} based on L-asparagine hydrolysis based on the Berthelot reaction. However, we have already explored this approach, and data and discussion on the difficulties it presents are included below. We propose to generate preliminary data regarding accuracy, repeatability, linearity and range by the end of 2011 for consideration by the FDA, and would wish to then discuss the next steps with FDA .

Does the Agency agree with this approach?

FDA Response: On the basis of your argument, the major issues with the Berthelot test method are to capture a low concentration gas (NH_3) and the limited sensitivity of ammonia detection at substrate concentration below the K_m . Given that these assay limitations may lead to inaccurate rate measurements and non-linearity of reaction time courses, the proposal to generate data on the accuracy, repeatability and range of the Berthelot reaction may only confirm that monitoring the release of ammonia lacks the robustness necessary for reliable K_m/k_{cat} measurements. Alternatively, monitoring the release of aspartic acid during L-asparagine hydrolysis would certainly be more amenable to quantitation, than the release of ammonia, through derivatization with fluorescent reagents. A plethora of reports on the fluorescent derivatization of amino acids, including aspartic acid, can be found in the scientific literature (e.g. Tcherkas and Denisenko, Journal of Chromatography A (2001), 913, 309-313). Please consider monitoring aspartic acid release during L-asparagine hydrolysis as a method for measuring the K_m/k_{cat} values of Erwinaze.

Discussion During 8/5/2011 Teleconference: EUSA Pharma acknowledged and agreed with FDA's response. There was no discussion during the meeting.

Q20: Although you evaluated the sub-visible particulate (SVP) content of the drug product at release and on stability using the USP <788> light obscuration test method, this test does not evaluate large protein particulates that are less than 10 μm in size. Given that protein aggregates of less than 10 μm present in therapeutic protein products may enhance immune responses to the active moiety, these product-related variants should be, to the extent possible, appropriately characterized and controlled. Furthermore, because the light obscuration test is relatively insensitive for detecting semi-translucent protein particles, additional orthogonal techniques should be employed to determine if the light obscuration test provides a reasonably accurate estimate of the content of these smaller sub-visible particulates. Since current analytical technologies can reliably quantitate particles that are (b) (4), your analysis of the SVP content should include data on the types and amounts of SVP in the (b) (4) range. We therefore request that you provide information on the types and amounts of these smaller sub-visible particulates (b) (4)

DRAFT

DRAFT

DRAFT

BLA 125359 – Erwinaze
TCON of August 5, 2011 with EUSA Pharma

(b) (4) *in the final drug product under real-time and stress stability conditions and determine the relative accuracy of the light obscuration method through the use of a sensitive orthogonal technique. Please include an assessment of the risk these particulates may pose to product quality, clinical safety and efficacy, and your strategy for controlling this risk.*

EUSA Pharma: We accept the FDA's request for more data on SVPs and will submit an experimental plan for the analytical studies by 4Q2011.

FDA Response: The proposal is acceptable.

Discussion During 8/5/2011 Teleconference: EUSA Pharma acknowledged and agreed with FDA's response. There was no discussion during the meeting.

Q21: Peptide mapping is one of the most powerful methods for identity and purity determinations. A well validated peptide mapping method provides valuable information on the sequence and structure (e.g., disulfide bridge, glycosylation and PEGylation sites) of the protein tested. Information on product-related impurities (e.g. oxidation and deamidation, protein sequence modifications and truncations) can also be obtained from the peptide map of the protein. Consistency in the manufacture of various DS/DP lots can be accurately assessed by comparing the peptide maps of such individual DS/DP lots with the peptide map of a DS/DP reference standard lot. Peptide maps are generated using endopeptidase(s) in order to fragment the protein to peptides, which may be separated by chromatographic techniques. More than one endopeptidase is usually required to provide overlapping peptide sequences and to cover ~98% of the total protein sequence. Selection of the endopeptidases (e.g. lys-C, glu-C, trypsin or a combination thereof) and the digestion conditions are critical to the quality of the peptide map. All the peptide fragments should optimally be base-line resolved by chromatography to permit accurate sequence determination and assessment of comparability with the peptide fragments of a reference standard generated under identical conditions. However, the peptide map of Erwinaze you presented shows many peptide fragment peaks overlapping with each other. Such a lack of chromatographic resolution between peptide fragments prevents a robust evaluation of the consistency in the manufacturing of the DS validation batches with that of the Erwinaze Reference Standard (ERS). Please submit a plan for revising the peptide mapping method used in the DS specifications that would produce chromatographically base-line resolved peptides for most fragments and account for ~98% of the protein sequence.

EUSA Pharma: We commit to revising the peptide mapping method used for DS and DP testing as requested. We will submit the validation report on the revised method by the end of September 2012.

FDA Response: The proposal is acceptable.

DRAFT

DRAFT

DRAFT

BLA 125359 – Erwinaze
TCON of August 5, 2011 with EUSA Pharma

Discussion During 8/5/2011 Teleconference: EUSA Pharma acknowledged and agreed with FDA's response. There was no discussion during the meeting.

Q22: 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) (b) (4) The rabbit pyrogen data and test results should be submitted in a CBE-0 by a date to be determined.

EUSA Pharma: On the basis of the current manufacturing schedule and the consequent availability of three batches of drug substance for testing the earliest time for submission of the report is the end of June 2012. Is this acceptable to FDA?

FDA Response: The proposal is acceptable.

Discussion During 8/5/2011 Teleconference: EUSA Pharma acknowledged and agreed with FDA's response. There was no discussion during the meeting.

Q23: 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.

EUSA Pharma: As mentioned above in the response to Question 15, a detailed protocol for method validation and study execution of a container-closure integrity test for samples on stability in lieu of sterility testing was submitted to FDA in BLA Amendment # 15 on the 27th April 2011. A copy is also attached to this response.

We commit to submit the data from the studies by 31st December 2011. Is this acceptable to FDA?

FDA Response: The proposal is acceptable.

Discussion During 8/5/2011 Teleconference: EUSA Pharma acknowledged and agreed with FDA's response. There was no discussion during the meeting.

Q24: Provide validation data from the executed protocol for shipping Erwinaze drug product from (b) (4) to the US market. Submit the data in a CBE-0 supplement by a date to be determined.

EUSA Pharma: We will submit the data from the executed protocol as requested, by the end of September 2011.

DRAFT

DRAFT

DRAFT

BLA 125359 – Erwinaze
TCON of August 5, 2011 with EUSA Pharma

FDA Response: Please see FDA response to shipping validation protocol deficiency. The approved protocol should be used to determine timelines.

Discussion During 8/5/2011 Teleconference: EUSA Pharma acknowledged and agreed with FDA's response. There was no discussion during the meeting.

Q25: 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.

EUSA Pharma: (b) (4) commits to implement the process improvements relating to the Extract manufacturing process. The improvements will be completed by the end of P122 extractions (scheduled for end February 2012). Once implemented, the bioburden and endotoxin data from the subsequent three extraction batches, which are scheduled to be manufactured in June 2012 will be submitted. The target date for submission of data from the three extractions will therefore be the end of July 2012.

FDA Response: The proposal is acceptable.

Discussion During 8/5/2011 Teleconference: EUSA Pharma acknowledged and agreed with FDA's response. There was no discussion during the meeting.

Q26: 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.

EUSA Pharma: We commit to monitor bioburden and endotoxin levels in CM6 pooled fractions, CM8 pooled fractions, and DEAE pooled fractions held for more than 24 hours at scale. This in-process hold study will be performed on the next three batches of drug substance which are to be manufactured (P121, P122 and P123). Batch P123 is scheduled for completion in October 2012. The target date for submission of data from the three batches will therefore be the end of November 2012.

FDA Response: The proposal is acceptable.

Discussion During 8/5/2011 Teleconference: EUSA Pharma acknowledged and agreed with FDA's response. There was no discussion during the meeting.

Q27: Qualification of the bioburden and endotoxin in-process test methods is not complete.

DRAFT

DRAFT

DRAFT

BLA 125359 – Erwinaze
TCON of August 5, 2011 with EUSA Pharma

- 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.*

EUSA Pharma: The target date for submission of the report on the qualification of the endotoxin assay using two additional batches of drug substance is by end July 2012. This date is based on the current production schedule. If the schedule is subject to significant alteration the Sponsor will notify the Agency in a timely manner.

FDA Response: The proposal is acceptable.

Discussion During 8/5/2011 Teleconference: EUSA Pharma acknowledged and agreed with FDA's response. There was no discussion during the meeting.

- 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.*

EUSA Pharma: The target date for submission of the report on the qualification of the bioburden assay using two additional batches of drug substance is end July 2012. This date is based on the current production schedule. If the schedule is subject to significant alteration the Sponsor will notify the Agency in a timely manner.

FDA Response: The proposal is acceptable.

Discussion During 8/5/2011 Teleconference: EUSA Pharma acknowledged and agreed with FDA's response. There was no discussion during the meeting.

Additional Discussion During 8/5/2011 Teleconference: EUSA Pharma asked whether outstanding items should be submitted on a rolling basis or as bundles. FDA stated they should be submitted in as few bundles as possible. EUSA Pharma advised they will submit in three bundles; a majority of the items will be included in the first bundle at the end of August, a smaller bundle in mid-September, and the remaining items included in a bundle at the end of September. FDA advised EUSA Pharma to identify (list) in the cover letter everything that is included in the August submission and also identify those items that would be submitted in the subsequent September submissions.

Regarding Moisture Content and Lyophilizer Validation: EUSA Pharma plans to submit the lyophilizer validation data as a PMC by 3rd quarter of 2012. FDA has concerns with current moisture monitoring based on testing of 4 vials per batch. FDA would like to see worst case lyophilizer locations identified, monitoring at these different locations, and moisture testing of

DRAFT

DRAFT

DRAFT

BLA 125359 – Erwinaze
TCON of August 5, 2011 with EUSA Pharma

more vials per load. EUSA Pharma agreed to submit a proposal for –moisture monitoring in the package at the end of August.

Regarding Media Fills: EUSA stated the most recent media fill results will be submitted at the end of September.

Regarding Shipping Protocol/Validation: FDA stated their concerns with the shipping validation. The validation in the BLA submission was done with empty vials. FDA wants to see a study with filled vials and the validation should address “worst-case” scenarios including duration, temperature, load configurations, etc., and should be performed with a commercial shipper that is adequately monitored for temperature with temperature probe placements throughout the load. EUSA Pharma stated their understanding of FDA’s concerns and will submit a shipping validation protocol by mid-September.

Regarding Stability Data: FDA would like to see an update for both Drug Product and Drug Substance if available stability data. EUSA Pharma plans to submit this data in the package at the end of August.



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

Memorandum

Date: 08/04/11

From: Norma Griffin, RPM DBOP/OODP/CDER/FDA

Subject: BLA STN 125359 (Erwinaze); FDA Response to EUSA Pharma's July 22, 2011, email document which contained responses to FDA's July 11, 2011, CMC Deficiencies Memo.

From: Griffin, Norma
Sent: Thursday, August 04, 2011 4:28 PM
To: 'Paul Plourde'; Tim Corn
Cc: Laughner, Erik
Subject: RE: 125359 Erwinaze - Friday's Call on Friday - FDA DRAFT Responses/Comments
Importance: High

Good Afternoon Paul/Tim,

Thanks for your patience as I was waiting on final approval. Please find attached the DRAFT FDA Responses for tomorrow's TCON for BLA 125359 Erwinaze.

Regarding our scheduled meeting, you have the following options:

If you feel that FDA's responses are clear, you have the option of cancelling the meeting (teleconference).

If you need minor clarification regarding FDA's comment(s), we may be able to resolve via email (if you choose) in lieu of the meeting.

If you choose to proceed with the meeting as scheduled, please let me know which questions/comments you want to focus on during the meeting so that we may make the most efficient use of our allotted time.

Please contact me if you have any questions and kindly respond to confirm receipt of this email and the attached DRAFT Responses/Comments.

Norma S. Griffin

Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Email: Norma.Griffin@fda.hhs.gov
Telephone 301.796.4255



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

Memorandum

Date: August 4, 2011
From: *Norma Griffin; Regulatory Project Manager, DBOP/OODP/OND/CDER/FDA*
Subject: **Draft Responses / Comments - BLA 125359 EUSA Pharma and "Erwinaze"**
Meeting of August 5, 2011 to Discuss CMC Deficiencies

Meeting Type: Teleconference
Meeting Category: Other - teleconference
Meeting Date and Time: August 5, 2011; 11:00 AM to 12:00 PM (ET)
Meeting Location: White Oak Building 22; Conference Room 3201
IND Number: BLA 125359
Product Name: Erwinaze
Sponsor Name: EUSA Pharma
Meeting Requestor: Paul Plourde - Senior Vice President, Global Medical
Oncology & US Medical Affairs Head
Meeting Chair: Barry Cherney
Meeting Recorder: Norma Griffin (for Erik Laughner)

TENTATIVE LIST OF FDA ATTENDEES:

Office of New Drugs
Office of Oncology Drug Products
Division of Biologic Oncology Drug Products
Joseph Gootenberg Deputy Division Director
Patricia Dinndorf Clinical Reviewer
Karen Jones Chief Project Management Staff
Norma Griffin (for Erik Laughner) Regulatory Project Manager

Office of Biotechnology Products
Division of Therapeutic Proteins
Amy Rosenberg Division Director
Barry Cherney Deputy Division Director
Serge Beaucage Product Quality Reviewer
Cristina Ausin Product Quality Reviewer
Jacek Cieslak Product Quality Reviewer
Nikolay Spiridonov Product Quality Reviewer

DRAFT

DRAFT

DRAFT

BLA 125359 – Erwinaze
TCON of August 5, 2011 with EUSA Pharma

Office of Compliance
Office of Manufacturing and Product Quality
Division of Good Manufacturing Practice Assessment
Patricia Hughes
Kalavati Suvarna
Mary Farbman

TENTATIVE LIST OF SPONSOR ATTENDEES:

EUSA
Tim Corn
Paul Plourde
Bill Bennett

Chief Medical Officer
Senior Vice President; clinical
Vice President of US Regulatory and QA



Consultant



Meeting Purpose: The purpose of this meeting is to discuss the deficiencies identified in the tertiary review from both DTP and DMPQ for the Erwinaze BLA.

These preliminary responses to CMC issues were sent to EUSA Pharma on August 4, 2011.

BLA 125359 – Erwinaze
TCON of August 5, 2011 with EUSA Pharma

Product

In regard to Erwinaze drug substance (DS) manufacturing process and process controls:

Q2: Your proposed DS release and stability acceptance criteria for specific activity is broader than your estimated manufacturing experience, based on the data submitted to the application. This acceptance criterion should ensure that you will consistently meet the expected quality attributes of the drug product. Please tighten this control to limits in line with any revision to the drug product specifications or provide a justification supported by data as to why this action is unnecessary.

EUSA Pharma: The specification originally proposed was (b) (4). In line with the revised limits proposed for drug product (see Question 6 below), EUSA will tighten the release specification for specific activity for drug substance to (b) (4). This would encompass the release data available for DS batches, each of which has been processed on to drug product batches.

In addition, we will establish separate release and stability specifications, and tighten the stability specification to (b) (4).

Does the Agency agree with these revisions?

FDA Response: Insufficient information was provided to evaluate the proposal. Understanding the process capability and defining limits based on a statistical analysis that provides some assurance that future lots will pass specification is a useful activity to assure manufacturability of the product. However, a statistical approach does not assess the potential impact to clinical performance at the allowable limits. Please include a justification for the proposed limits based on the impact to clinical performance and provide the data that support this assessment.

Q3: The drug substance specification of “Comparable to ERS (Erwinaze Reference Standard)” for the peptide mapping method does not include objective criteria to assess what “comparable to reference standard” actually means. Objective criteria allow for consistent evaluation of product quality and should be established whenever the acceptance criteria are based on a comparison to a reference material. Please revise the acceptance criteria to include limits on the following: selected peak heights; peak areas; and peak retention times to ensure comparability to the ERS. In addition, limits on new peaks not observed in the ERS should be set based on a defined percentage of the total peak area.

EUSA Pharma: We will revise the acceptance criteria for peptide mapping for drug substance as requested. In addition, and as requested in Question 12, we will include these same criteria in the peptide mapping release test for drug product.

BLA 125359 – Erwinaze

TCON of August 5, 2011 with EUSA Pharma

Does the Agency agree with these revisions?

FDA Response: The proposed revisions are acceptable with the exception of the proposed acceptance criteria for new peaks in Unknowns, which are not present in ERS. A peak area of (b) (4) of the total peak area for each new peak is too high considering that these peaks results from the proteolytic fragmentation of a commensurately abundant species, the peptide fragments of which may or may not overlap with those of Erwinaze peptide fragments. A tighter control on the allowable peak area of new peaks other than those of the ERS is required to provide adequate assurance of the identity and purity of Erwinaze DS/DP. It may be acceptable to include an action limit that will initiate an investigation into the potential impact of a new impurity when observed in the peptide map.

Q4: Regarding your validation of impurity removal: the general approach you have taken was to obtain in-process samples at different manufacturing stages ((b) (4) (b) (4)) during the manufacture of the three process validation batches, and then determine the level of impurities in these materials. The data from these analyses show that the purification process has adequately removed the various impurities evaluated. For example, you have shown that (b) (4) are cleared to levels below the detection limit of the assay in bulk DS. However, validation batches are manufactured to the target operating parameters and provide little information on product quality when the process is operated at the allowable extremes of these parameters or when there is considerable variability in the input impurity load (e.g., host cell protein or DNA). In these situations, assessment of the capacity of the manufacturing process to clear impurities at the allowable extremes of the in-process parameters plays an important role in evaluating the robustness of a purification process for clearing process related impurities. This is viewed as an integral component in validating impurity clearance and eliminating routine testing for that impurity at release. In some cases, a demonstration that the process has excess clearance capacity (i.e., through the use of laboratory spiking studies) may be used in lieu of worst case studies. Please include impurity testing in the release specifications or provide additional data supporting, with a high degree of confidence based on robustness testing, that the process will clear the impurities. Impurities include (b) (4)!

EUSA Pharma: We will include tests for host cell protein and DNA in the release specification for drug substance. We will include testing for (b) (4)

Does the Agency agree with this approach?

DRAFT

DRAFT

DRAFT

BLA 125359 – Erwinaze
TCON of August 5, 2011 with EUSA Pharma

FDA Response: Specification limits for the above impurities should be established on the basis of the purification process capability and on the historical test results for these impurities along with an understanding of the potential impact to clinical performance. The proposed specification limits for (b) (4) than the actual test results for the impurities. These limits are not representative of the capability of the purification process and not in line with clinical experience; the proposed specification limits for (b) (4) (b) (4) should therefore be tightened.

Regarding the Erwinaze drug product (DP) manufacturing process and process controls:



(b) (4)

BLA 125359 – Erwinaze
TCON of August 5, 2011 with EUSA Pharma

(b) (4)

Q20: Although you evaluated the sub-visible particulate (SVP) content of the drug product at release and on stability using the USP <788> light obscuration test method, this test does not evaluate large protein particulates that are less than 10 µm in size. Given that protein aggregates of less than 10 µm present in therapeutic protein products may enhance immune responses to the active moiety, these product-related variants should be, to the extent possible, appropriately characterized and controlled. Furthermore, because the light obscuration test is relatively insensitive for detecting semi-translucent protein particles, additional orthogonal techniques should be employed to determine if the light obscuration test provides a reasonably accurate estimate of the content of these smaller sub-visible particulates. Since current analytical technologies can reliably quantitate particles that are (b) (4), your analysis of the SVP content should include data on the types and amounts of SVP in the (b) (4) size range. We therefore request that you provide information on the types and amounts of these smaller sub-visible particulates (b) (4) (b) (4) in the final drug product under real-time and stress stability conditions and determine the relative accuracy of the light obscuration method through the use of a sensitive orthogonal technique. Please include an assessment of the risk these particulates

DRAFT

DRAFT

DRAFT

BLA 125359 – Erwinaze

TCON of August 5, 2011 with EUSA Pharma

may pose to product quality, clinical safety and efficacy, and your strategy for controlling this risk.

EUSA Pharma: We accept the FDA's request for more data on SVPs and will submit an experimental plan for the analytical studies by 4Q2011.

FDA Response: The proposal is acceptable.

Q21: Peptide mapping is one of the most powerful methods for identity and purity determinations. A well validated peptide mapping method provides valuable information on the sequence and structure (e.g., disulfide bridge, glycosylation and PEGylation sites) of the protein tested. Information on product-related impurities (e.g. oxidation and deamidation, protein sequence modifications and truncations) can also be obtained from the peptide map of the protein. Consistency in the manufacture of various DS/DP lots can be accurately assessed by comparing the peptide maps of such individual DS/DP lots with the peptide map of a DS/DP reference standard lot. Peptide maps are generated using endopeptidase(s) in order to fragment the protein to peptides, which may be separated by chromatographic techniques. More than one endopeptidase is usually required to provide overlapping peptide sequences and to cover ~98% of the total protein sequence. Selection of the endopeptidases (e.g. lys-C, glu-C, trypsin or a combination thereof) and the digestion conditions are critical to the quality of the peptide map. All the peptide fragments should optimally be base-line resolved by chromatography to permit accurate sequence determination and assessment of comparability with the peptide fragments of a reference standard generated under identical conditions. However, the peptide map of Erwinaze you presented shows many peptide fragment peaks overlapping with each other. Such a lack of chromatographic resolution between peptide fragments prevents a robust evaluation of the consistency in the manufacturing of the DS validation batches with that of the Erwinaze Reference Standard (ERS). Please submit a plan for revising the peptide mapping method used in the DS specifications that would produce chromatographically base-line resolved peptides for most fragments and account for ~98% of the protein sequence.

EUSA Pharma: We commit to revising the peptide mapping method used for DS and DP testing as requested. We will submit the validation report on the revised method by the end of September 2012.

FDA Response: The proposal is acceptable.

Q22: 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)

DRAFT

DRAFT

DRAFT

BLA 125359 – Erwinaze
TCON of August 5, 2011 with EUSA Pharma

(b) (4) The rabbit pyrogen data and test results should be submitted in a CBE-0 by a date to be determined.

EUSA Pharma: On the basis of the current manufacturing schedule and the consequent availability of three batches of drug substance for testing the earliest time for submission of the report is the end of June 2012. Is this acceptable to FDA?

FDA Response: The proposal is acceptable.

Q23: 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.

EUSA Pharma: As mentioned above in the response to Question 15, a detailed protocol for method validation and study execution of a container-closure integrity test for samples on stability in lieu of sterility testing was submitted to FDA in BLA Amendment # 15 on the 27th April 2011. A copy is also attached to this response.

We commit to submit the data from the studies by 31st December 2011. Is this acceptable to FDA?

FDA Response: The proposal is acceptable.

Q24: Provide validation data from the executed protocol for shipping Erwinaze drug product from (b) (4) to the US market. Submit the data in a CBE-0 supplement by a date to be determined.

EUSA Pharma: We will submit the data from the executed protocol as requested, by the end of September 2011.

FDA Response: Please see FDA response to shipping validation protocol deficiency. The approved protocol should be used to determine timelines.

Q25: 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.

EUSA Pharma: (b) (4) commits to implement the process improvements relating to the Extract manufacturing process. The improvements will be completed by the end of P122 extractions (scheduled for end February 2012). Once implemented, the bioburden and endotoxin data from the subsequent three extraction batches, which are scheduled to be manufactured in June 2012 will be submitted. The target date for submission of data from the three extractions will therefore be the end of July 2012.

DRAFT

DRAFT

DRAFT

BLA 125359 – Erwinaze
TCON of August 5, 2011 with EUSA Pharma

FDA Response: The proposal is acceptable.

Q26: 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.

EUSA Pharma: We commit to monitor bioburden and endotoxin levels in CM6 pooled fractions, CM8 pooled fractions, and DEAE pooled fractions held for more than 24 hours at scale. This in-process hold study will be performed on the next three batches of drug substance which are to be manufactured (P121, P122 and P123). Batch P123 is scheduled for completion in October 2012. The target date for submission of data from the three batches will therefore be the end of November 2012.

FDA Response: The proposal is acceptable.

Q27: 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.*

EUSA Pharma: The target date for submission of the report on the qualification of the endotoxin assay using two additional batches of drug substance is by end July 2012. This date is based on the current production schedule. If the schedule is subject to significant alteration the Sponsor will notify the Agency in a timely manner.

FDA Response: The proposal is acceptable.

- 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.*

EUSA Pharma: The target date for submission of the report on the qualification of the bioburden assay using two additional batches of drug substance is end July 2012. This date is based on the current production schedule. If the schedule is subject to significant alteration the Sponsor will notify the Agency in a timely manner.

FDA Response: The proposal is acceptable.



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

Memorandum

Date: 07/15/11 *ESL 07/15/11*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: EUSA Pharma (STN 125359/0); tcon regarding proposal to perform analysis of new archived samples for asparaginase in support of BLA.

FDA ATTENDEES: Erik Laughner, Patricia Keegan, Patricia Dinndorf, Suzanne Demko, Jun Yang, Hong Zhao, Charles Bonapace, Mike Skelly

EUSA PHARMA ATTENDEES:

Tim Corn, MD Chief Medical Officer EUSA
Paul Plourde MD SVP, Erwinase Team Leader
Bill Bennett VP Regulatory and QA EUSA US

(b) (4)

Russ Wolz, PHD Asparaginase Team Leader

(b) (4)

BACKGROUND: On July 8, 2011, EUSA Pharma provided a short written proposal via email which contained an analysis plan to test archived immunogenicity samples for asparinases in order to establish meaningful clinical data in support of the BLA. On July 11, 2011 EUSA Pharma provided via email a list of corresponding questions to FDA. FDA provide EUSA Pharma responses via email on July 14, 2011 in advance of this scheduled teleconference.

DISCUSSION: (actual telecon discussion is captured below EUSA Pharma's original questions and FDA's written response)

Question #1

The sponsor is proposing to take a subset of the stored frozen immunoassay serum samples from Course 1 (AB-02) to corroborate the (b) (4) asparaginase activity data submitted in the BLA. These samples were not taken at time points identical to the samples analyzed for the primary and secondary asparaginase endpoints in the protocol but do represent 48 and 72 hour trough values.

Does the Agency agree that these samples adequately reflect endpoint conditions?

FDA Response: The proposal to "corroborate" the (b) (4) activity data is not acceptable as the inspectional findings have demonstrated that the assay was not performed under appropriately controlled conditions, rendering the data unreliable. Based on the information you have provided, there are serum samples available for 29 patients at the 48-hour timepoint and for 12 patients at the 72-hour timepoint pre Dose 4. Please re-assay these serum samples using the (b) (4)

Laboratories assay methodology and provide the asparaginase activity results in support of your BLA.

Discussion During the Teleconference: FDA reiterated that EUSA Pharma should not focus on any efforts corroborating the (b)(4) lab data. That data was deemed unusable. EUSA Pharma acknowledged. FDA confirmed that the sample timepoints outlined above appeared to be satisfactory in terms of measuring asparaginase trough levels.

Question 2

The analyses will be done by (b)(4) under GLP conditions. Their asparaginase activity assay has been validated and the validation results were submitted by another Sponsor to the Agency. The Agency has reviewed and accepted the assay and its validation. Because the assay was developed to measure asparaginase activity of pegaspargase in plasma, this form of asparaginase was used as the standard in the validation and is used as standard in routine commercial execution of the assay. The vehicle for QC and analyte samples is plasma. EUSA is planning for (b)(4) to use native *E. coli* derived asparaginase as standard and serum as sample vehicle for the analyses of the AB-02 samples since this will reproduce the critical analytical conditions used in the (b)(4) assays. A formal GLP qualification study will be executed prior to analysis of the AB-02 samples to ensure that the change in standard and sample vehicle does not impact the assay validation.

Is this acceptable to the Agency?

FDA Response: We agree that it would be prudent to conduct a partial or mini-validation prior to testing patient samples. In your response to the FDA-identified deficiencies, in addition to providing the results of the validation, please provide data to establish the comparability of the methodology and comparable calibration to the Asselin method which was used to establish the clinical relevance of the proposed asparaginase trough levels.

Discussion During the Teleconference: EUSA Pharma noted that bridging studies would not be performed. Rather full validation would be completed prior to any samples being run. EUSA Pharma proposed to provide FDA with a protocol within a few weeks for review. FDA acknowledged.

Question #3

The proportion of patients having an asparaginase activity level of ≥ 0.1 IU/mL as measured by (b)(4) (b)(4) will be calculated for both the 48 and 72 hour trough AB-02 samples. These proportions will then be compared to the proportions of patients meeting the same criteria as measured by the (b)(4) in its analysis of the PK-06 samples, and in its analysis of the primary and secondary asparaginase endpoints as reported in the BLA. A comparable outcome will be considered corroboration of both the (b)(4) data generally and the asparaginase endpoint analysis specifically.

Is this acceptable to the Agency?

FDA Response: Please provide the results of the (b) (4) assay for each patient sample. As stated in our response to question 1, the (b) (4) data is not considered valid or reliable based on the deficiencies identified on the FDA inspection of this clinical laboratory site; therefore the corroboration of the (b) (4) results with the (b) (4) results are not appropriate.

Discussion During the Teleconference: EUSA Pharma acknowledged and there was no further discussion.

Question #4

The Sponsor would like to submit the reports for the qualification of the assay and for the analysis of AB-02 samples as an amendment to the BLA. This amendment would include the report and an Excel file of the data. Given the small number of samples and the straightforward analysis we do not plan to have formal TLs or to do any hyperlinking to the (b) (4) data.

Is this acceptable to the Agency?

FDA Response: It is acceptable to provide the (b) (4) assay results in an excel spreadsheet. It will not be necessary to resubmit or hyperlink to the (b) (4) data.

Discussion During the Teleconference: EUSA Pharma acknowledged. EUSA Pharma proposed to provide FDA with a mock-up of the proposed data submission once the assays were complete. FDA acknowledged and noted that full demographics on the specific patients should be provided.

Question #5

As stated in prior communications, we are under considerable financial pressure and would like to request an accelerated review and response both on this proposal and on the validity of the data in the BLA submission.

Can the Agency review these limited data before the end of August?

FDA Response: We cannot commit to a specific review timeframe, as this is contingent upon the timing of the submission to FDA and completeness of the data.

Discussion During the Teleconference: EUSA Pharma acknowledged and noted that (b) (4) (b) (4) were notified that they would be likely inspected by FDA. EUSA Pharma inquired whether the archived sample storage site would likely be audited. FDA requested that EUSA Pharma attest in writing that the storage facility freezer storing the samples did not have any excursions in temperature. FDA also requested that EUSA Pharma obtain from CTEP/CRO the auditing procedures for ensuring sample integrity. FDA would review and make a final determination of whether that site should be inspected or not.

Could the DSI inspection of (b) (4) planned by the FDA be scheduled the week after (b) (4)

FDA Response: At this time we cannot commit to specific dates for possible inspections.

However, we will appreciate receiving a copy of the (b) (4) report for partial assay validation or qualification using native *E. coli* asparaginase and serum for calibrators and quality control samples. Furthermore we will appreciate receiving interim reports on their progress in the analyses, so that we can schedule inspections accordingly.

Discussion During the Teleconference: EUSA Pharma acknowledged

ADDITIONAL MEETING DISCUSSION:

EUSA Pharma confirmed that the (b) (4) was reviewing FDA's recent CMC deficiency list and that a written response would be provided the end of next week. EUSA Pharma acknowledged that FDA was amenable to a tcon regarding CMC upon receipt of those responses.



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

Memorandum

Date: 07/14/11 82 07/14/11
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: EUSA Pharma (STN 125359/0); tcon regarding review status of application

DISCUSSION:

Paul Plourde called to inquire about the upcoming July 15, 2011, tcon to discuss the new assay analysis proposal (provided on July 7, 2011 via email) of the archived samples from (b) (4). I noted that FDA would be providing written responses later today to their subsequent list of questions (provided on July 11, 2011 via email) in advance of the tcon.

Paul noted that they were continuing to review FDA's CMC deficiency list provided on July 11, 2011 and would be providing a written response by July 22, 2011. Paul requested a tcon be arranged either July 26, 27, 28 to discuss the responses. I acknowledged this was possible and agreed to arrange.

I noted that once FDA and EUSA Pharma could agree to the plan/timelines for the new clinical data as well as resolving the CMC issues, an estimate for a final review period could be possibly discussed. I inquired on the status of the proposed Proper Name for the BLA and Paul noted that as USAN was reluctant to use the nonsensical prefix, they would rely on FDA to assign the Proper Name at the time of approval per the regulations.



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

Memorandum

Date: 07/14/11

ESL
07/19/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: EUSA Pharma (USA); BLA STN 125359/0; Response to Questions Regarding
New Analysis of Samples for PK Measurement

From: Laughner, Erik
Sent: Thursday, July 14, 2011 9:32 AM
To: 'Paul Plourde'
Subject: STN 125359; Response to Questions Regarding New Analysis of Samples for PK Measurement
Importance: High

Paul,

Please see FDA's responses to your questions in advance of the tcon tomorrow. Please confirm receipt.

Sincerely,

Erik



071411 FDA
esponse to questio..

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

If you have received this message in error, do not use, disclose, reproduce, or distribute this message (including any attachments) and notify me immediately. Thank you.



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

Memorandum

Date: July 14, 2011
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: FDA Request for Information; BLA STN 125359 (Erwinaze); Response to EUSA Pharma information requests regarding analysis of archived immunoassay samples for determination of asparaginase activity.

The following are FDA's responses to your requests provided on July 11, 2011 in advance of the July 15, 2011 teleconference:

Questions to FDA on the Proposal Submitted to Corroborative the (b) (4) Asparaginase Activity Sample Analysis

Question #1

The sponsor is proposing to take a subset of the stored frozen immunoassay serum samples from Course 1 (AB-02) to corroborate the (b) (4) asparaginase activity data submitted in the BLA. These samples were not taken at time points identical to the samples analyzed for the primary and secondary asparaginase endpoints in the protocol but do represent 48 and 72 hour trough values.

Does the Agency agree that these samples adequately reflect endpoint conditions?

FDA Response: The proposal to "corroborate" the (b) (4) activity data is not acceptable as the inspectional findings have demonstrated that the assay was not performed under appropriately controlled conditions, rendering the data unreliable. Based on the information you have provided, there are serum samples available for 29 patients at the 48-hour timepoint and for 12 patients at the 72-hour timepoint pre Dose 4. Please re-assay these serum samples using the (b) (4) assay methodology and provide the asparaginase activity results in support of your BLA.

Question 2

The analyses will be done by (b) (4) under GLP conditions. Their asparaginase activity assay has been validated and the validation results were submitted by another Sponsor to the Agency. The Agency has reviewed and accepted the assay and its validation. Because the assay was developed to measure asparaginase activity of pegaspargase in plasma, this form of asparaginase was used as

the standard in the validation and is used as standard in routine commercial execution of the assay. The vehicle for QC and analyte samples is plasma. EUSA is planning for (b) (4) to use native *E. coli* derived asparaginase as standard and serum as sample vehicle for the analyses of the AB-02 samples since this will reproduce the critical analytical conditions used in the (b) (4) assays. A formal GLP qualification study will be executed prior to analysis of the AB-02 samples to ensure that the change in standard and sample vehicle does not impact the assay validation.

Is this acceptable to the Agency?

FDA Response: We agree that it would be prudent to conduct a partial or mini-validation prior to testing patient samples. In your response to the FDA-identified deficiencies, in addition to providing the results of the validation, please provide data to establish the comparability of the methodology and comparable calibration to the Asselin method which was used to establish the clinical relevance of the proposed asparaginase trough levels.

Question #3

The proportion of patients having an asparaginase activity level of ≥ 0.1 IU/mL as measured by (b) (4) will be calculated for both the 48 and 72 hour trough AB-02 samples. These proportions will then be compared to the proportions of patients meeting the same criteria as measured by the (b) (4) laboratory in its analysis of the PK-06 samples, and in its analysis of the primary and secondary asparaginase endpoints as reported in the BLA. A comparable outcome will be considered corroboration of both the (b) (4) data generally and the asparaginase endpoint analysis specifically.

Is this acceptable to the Agency?

FDA Response: Please provide the results of the (b) (4) assay for each patient sample. As stated in our response to question 1, the (b) (4) data is not considered valid or reliable based on the deficiencies identified on the FDA inspection of this clinical laboratory site; therefore the corroboration of the (b) (4) results with the (b) (4) results are not appropriate.

Question #4

The Sponsor would like to submit the reports for the qualification of the assay and for the analysis of AB-02 samples as an amendment to the BLA. This amendment would include the report and an Excel file of the data. Given the small number of samples and the straightforward analysis we do not plan to have formal TLs or to do any hyperlinking to the (b) (4) data.

Is this acceptable to the Agency?

FDA Response: It is acceptable to provide the (b) (4) assay results in an excel spreadsheet. It will not be necessary to resubmit or hyperlink to the (b) (4) data.

Question #5

As stated in prior communications, we are under considerable financial pressure and would like to request an accelerated review and response both on this proposal and on the validity of the data in the BLA submission.

Can the Agency review these limited data before the end of August?

FDA Response: We cannot commit to a specific review timeframe, as this is contingent upon the timing of the submission to FDA and completeness of the data.

Could the DSI inspection of (b) (4) planned by the FDA be scheduled the week after (b) (4)

FDA Response: At this time we cannot commit to specific dates for possible inspections. However, we will appreciate receiving a copy of the (b) (4) report for partial assay validation or qualification using native *E. coli* asparaginase and serum for calibrators and quality control samples. Furthermore we will appreciate receiving interim reports on their progress in the analyses, so that we can schedule inspections accordingly.



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

Memorandum

Date: 07/11/11 Esc 07/11/11
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: EUSA Pharma (USA); BLA STN 125359/0; Information Request/Advice re :
asparaginase analysis of archived immunogenicity samples.

From: Laughner, Erik
Sent: Monday, July 11, 2011 2:21 PM
To: 'Paul Plourde'
Subject: STN 125359; Advice Comments; Proposal to Evaluate Asapargainase Activity from Archive Immunogenicity Samples.
Importance: High

Hello Paul,

At this time, we provide the following advice comments on the proposed pharmacokinetic analysis of recently identified samples for evaluation of asparaginase activity.

Please confirm receipt.

Sincerely,

Erik



071111 IR PK
analysis Recommen..

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

If you have received this message in error, do not use, disclose, reproduce, or distribute this message (including any attachments) and notify me immediately. Thank you.



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

Memorandum

Date: July 11, 2011 *ESL 07/11/11*
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: FDA Request for Information; BLA STN 125359 (Erwinaze);
Advice/Recommendations for Analysis of Archived Clinical Samples for
Evaluation of Asparaginase Activity.

The following are FDA's recommendations regarding the proposal to evaluate the asparaginase activity of stored immunogenicity samples:

1. **Comparability of Methods:** The methodology for the asparaginase assays should be comparable to the methodology used to establish the primary surrogate efficacy criterion for the study, originally 48 hour trough activity ≥ 100 mU/mL. DBOP previously accepted the proposal to use an adaptation of the coupled enzymatic activity method reported by Asselin et al. (J. Clin. Oncol. 11:1780-1786, 1993). Thus, the operating principle of the method, the assay conditions, and calibration should be the same or comparable, and substantial differences should be defended. The method should have a validation report describing fundamental parameters including linear range, accuracy, precision, stability of reagents and samples under the conditions anticipated or employed during the study and analyses.
2. **Acceptance Criteria:** A Standard Operating Procedure should be established, describing the criteria to accept or reject an analytical run of patient samples, using quality control (QC) samples to demonstrate the validity of accepted runs. Runs not meeting these criteria should be repeated if possible, but the invalid data should be excluded from evaluations.
3. **Adequacy of Sample Timing:** According to EUSA Pharma, the serum samples stored from study AALL07P2, and originally intended for immunogenicity assays, were obtained pre-course and on Days 8 and 22 during dosing course #1 and pre-course, pre-dose 6, and Day 15 during subsequent courses. Information needs to be provided to the Agency to confirm that 1) samples are available for analysis that were obtained approximately 48 hours after the previous dose and 2) samples on Day 8 of course #1 were obtained prior to dosing.

4. **Documentation of Conditions during Shipping and Storage:** Documentation should be available from (b) (4), (b) (4) and the proposed analytical site describing the conditions of study samples during shipping and storage at both sites.
5. **Records of Freezer Temperatures:** Records of freezer temperatures at (b) (4) and the proposed analytical site should be available in a retrievable form to confirm that samples were stored and handled appropriately. If unanticipated variations such as accidental thawing occurred, either the variations should be defended with data to establish validity of bioanalytical data, or defective data should be excluded from analysis.
6. **Documentation of Sample Handling:** Records should be available from the proposed analytical site to establish when samples were removed from freezer storage for analysis, the condition of samples while thawed, and when samples were returned to the freezer.
7. **Documentation of Solutions:** Documentation at the analytical site should describe the preparation, storage, and stability of reagents including asparaginase stock solutions used to prepare calibration standards and quality control samples.



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

Memorandum

Date: 07/11/11

Σκ 07/11/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: EUSA Pharma (USA); BLA STN 125359/0; Information Request/Advice re :
CMC deficiencies

From: Laughner, Erik
Sent: Monday, July 11, 2011 9:20 AM
To: 'Paul Plourde'
Subject: STN 125359; CMC deficiencies
Importance: High

Hello Paul,

As discussed, FDA provides the following deficiencies identified for CMC. **They are divided up between pre-approval and PMC related.**

Please review and a tcon can be arranged to discuss timeframes etc.

Please confirm receipt.

Sincerely,

Erik



071111 CMC
eficiency Memo.doc.

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA

301-796-1393

erik.laughner@fda.hhs.gov

<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

If you have received this message in error, do not use, disclose, reproduce, or distribute this message (including any attachments) and notify me immediately. Thank you.



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

Memorandum

Date: July 11, 2011
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: FDA Request for Information; BLA STN 125359 (Erwinaze); CMC
Deficiencies

The following product and facility issues identified below must be addressed prior
to any approval action:

Product

[Redacted content]

(b) (4)

[Redacted content]

(b) (4)



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

Memorandum

Date: 07/07/11 *SL 07/09/11*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: EUSA Pharma (STN 125359/0); tcon regarding review status of application

DISCUSSION:

Paul Plourde called to note that EUSA Pharma was finishing up a brief written proposal on evaluation of archived immunogenicity samples for asparaginase determination. An expedited tcon was requested. I acknowledged and noted that FDA would need some time to internally review the proposal prior to a tcon, but agreed that this could be expedited for later in the following week. I informed Paul that FDA had met internally and re-confirmed that the data collected at the (b)(4) PK site was not reliable and could not be salvaged. EUSA Pharma should devote their resources to the proper analysis of any archived samples that could demonstrate appropriate PK measurement. FDA would be providing some written advice to EUSA Pharma to help ensure the new analysis did not suffer from the same issues as at the (b)(4) site. Paul acknowledged.

I also noted that FDA was completing a final review of the outstanding issues with respect to CMC for the BLA and would be providing as discussed at the June 23, 2011 meeting, a list of those deficiencies. FDA could arrange a tcon to discuss after EUSA Pharma (b)(4) had a chance to review. Paul acknowledged.



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

Memorandum

Date: 06/23/11

ESL 06/23/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: EUSA Pharma (STN 125359/0); Special meeting between EUSA Pharma and FDA to discuss serious pre-approval issues.

FDA ATTENDEES: Erik Laughner, Patricia Keegan, Patricia Dinndorf, Suzanne Demko, Jun Yang, Hong Zhao, Charles Bonapace, Mike Skelly, Dubravka Kufrin, Valerie Jensen, Emily Thakur, Mary Farbman, Patricia Hughes, Joseph Gootenberg, Greg Reaman, Kalavati Survarna

EUSA PHARMA ATTENDEES:

Tim Corn, MD Chief Medical Officer EUSA
Paul Plourde MD SVP, Erwinase Team Leader

(b) (4)

BACKGROUND: Based on serious DSI inspectional findings at the clinical pharmacology analytical site for the asparginase level determinations as well as FDA identified CMC deficiencies that would need addressed prior to BLA approval, FDA and EUSA Pharma agreed to a special meeting. This was not a formal PDUFA meeting and the minutes below are reflected only as a summary for the record.

DISCUSSION:

EUSA Pharma read a formal statement noting that Erwinase has been approved in many countries for many years. While not a "blockbuster" drug, it has a critical need in a limited population.

(b) (4)

EUSA Pharma stated that it was their opinion that the DSI clinical pharmacology central lab inspection in (b) (4) had resulted in identified deficiencies but that those were adequately addressed in the response submitted to the BLA. EUSA Pharma noted that FDA had previously agreed the asparagine data was unreliable so any identified issues with that analysis should be ignored. The asparginase data was robust and reliable.

EUSA Pharma also believed that the CMC inspection at the (b) (4) did not identify any major problems and that any changes/improvements requested by FDA could be handled as post-marketing commitments. EUSA Pharma noted that the (b) (4)

(b) (4)

(b) (4) had been retained to assist with addressing the CMC issues identified by FDA. EUSA Pharma also noted that FDA's Office of Compliance had recently found the (b) (4) facility acceptable via a formally issued letter.

FDA's facility group clarified that while the Office of Compliance might find the facility itself acceptable, the acceptability of manufacture of Erwinaze as it relates to the BLA was a separate issue. Issuance of an OAI was only for already approved products. FDA noted that there were a number of manufacturing issues identified by both the product and facility groups that would have to be resolved prior to approval. FDA agreed to provide EUSA Pharma a written list. A teleconference could then be scheduled to discuss.

FDA stated that based on the findings by DSI at the (b) (4) site, the asparaginase data was determined to be invalid and could not be relied on. The lab site did not adhere to good laboratory practices, especially concerning the way the critical standards/controls were used/maintained. FDA stated they were surprised the findings identified were downplayed by EUSA Pharma as minor. FDA stated that as the asparaginase data was the only efficacy data for the BLA, EUSA Pharma would need to repeat the study in a limited fashion to validate that Erwinaze could reduce asparaginase in serum.

FDA inquired whether EUSA Pharma could reactivate the COG study to enroll more patients and EUSA Pharma noted this was not possible given the time and costs involved. FDA inquired whether any archived samples either from the COG study or the Treatment Protocol were available for PK analysis. EUSA Pharma noted that they would have to look into this possibility.

FDA inquired whether a delay in issuance of the Complete Response letter would be beneficial for EUSA Pharma in terms of keeping the company viable long enough to work through the identified issues that must be resolved prior to any approval. EUSA Pharma noted that they would have to discuss with their board, but appreciated the possibility. FDA also noted they could possibly assist with the (b) (4) if that was helpful for preserving limited resources. EUSA Pharma acknowledged.

FDA agreed to work with EUSA Pharma on resolving the clinical pharmacology and CMC deficiencies. FDA agreed to provide in writing, the list of all the CMC issues that would be required to be fixed prior to any BLA approval. FDA agreed that short teleconferences could be arranged in the future to assist EUSA Pharma in providing the necessary data.

Attachment: Sign-in sheet for face-to-face meeting.

**DBOP meeting with EUSA Pharma (US)
Attendance Sheet**

Location: WO22, Room 1417
Time: 11:00 AM-3 12:00 PM ET

Date: June 23, 2011

Name:	Organization:
1. DR TIM CORN	EUSA Pharma
2. [REDACTED]	(b) (4)
3. Paul Ploarda MD	EUSA PHARMA
4. Patricia Duvdars	DBOP/ODDP/CDER
5. Gregory Reaman	IO/ODDP/CDER
6. JOE GOOTENBERG	DBOP/ODDP/CDER
7. Kalavati Sevarna	oc/DMPA/BMAB
8. PATRICIA HOAHAS	oc/DMPA/DGMPA/BMAB
9. Mary Farbman	OC/DMPQ/DGMPA/BMAB
10. Denahi Dubravka Kufnin	DBOP/ODDP/CDER
11. CHARLES BONAPACE	OC/OSI/CDER
12. Michael Skelly	OC/OSI
13. Valerie Jensen	Drug Shortage
14. Anne Pibon	FDA/ODDP/DBOP/CDER
15. Hong Zhao	FDA/CDER/OTS/OLP/DCPS
16. PATRICIA KEEGAN	FDA/CDER/ODDP/DBOP
17. Emily Thakur	FDA/CDER/Drug Shortage
18. Jun Yang	FDA/CDER/OTS/OLP/DCPS
19.	
20.	
21.	
22.	
23.	
24.	
25.	
26.	
27.	



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

Memorandum

Date: 05/27/11

ESL 05/27/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: EUSA Pharma (STN 125359/0); tcon regarding review status of application

DISCUSSION:

Paul Plourde called to request an update on the review status of the BLA and when any labeling might be provided for discussion. I indicated that the primary reviews for the application were being completed and that per our May 3, 2011, teleconference, there was no specific date of when proposed draft labeling might be provided for review. The Division was working towards completing the review of the BLA before the PDUFA action date. Dr. Plourde inquired whether FDA had completed the assessment of EUSA Pharma's response regarding the negative findings of the DSI inspection at the clinical pharmacology analytical site. I indicated that no information could be provided at this time.

Dr. Plourde noted that while EUSA Pharma was hopeful for a positive regulatory outcome of the review of the BLA, an unfavorable opinion requiring more than 3 months of work to resolve would likely result in a rapid discontinuation of the active IND treatment protocol

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

treatment protocol. Dr. Plourde anticipated that patients currently being treated might be allowed to continue therapy, but any new enrollment would have to be terminated. I acknowledged the impact this decision might have.



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

Memorandum

Date: May 17, 2011 *Er 05/17/11*
From: Erik Laughner, DBOP/OODP/CDER
Subject: BLA STN 125359 Erwinaze; Standing Monthly Team Meeting

Regulatory Management

Erik Laughner
Patricia Keegan (Director, DBOP)

Clinical

Patricia Dinndorf

Nonclinical

Dubravka Kufrin
Anne Pilaro (TL)

Clinical Pharmacology

Jun Yang

Facilities

Mary Farbman
Anastasia Lolas

Product

Jacek Cieslak
Serge Beaucage
Faruk Sheikh (immunogenicity)
Susan Kirshner (immunogenicity TL)
Kim Rains (OBP Labeling Reviewer)

DBOP Safety Team

Jeff Summers (DDS)
Grace Carmouze (sRPM)

OSE

Sue Kang
Loretta Holmes

Discussion: Participants were present from all disciplines. This monthly standing meeting provided reviewers/teams opportunity to discuss review status of BLA.



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

Memorandum

Date: 05/03/11 *ESL 05/3/11*

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: EUSA Pharma (STN 125359/0); tcon regarding regulatory issues

EUSA Pharma Attendees:

Tim Corn, MD -Chief Medical Officer
Paul Plourde MD -Erwinase Project Leader

DISCUSSION:

Paul Plourde called me along with Tim Corn to discuss the teleconference just held earlier today with Dr. Keegan regarding the review of the BLA. In response to a request for clarification on "what was in a BLA action letter", I clarified that two outcomes, approval or CR were possible as an action for a BLA. The CR was akin to a clinical hold for an IND whereby FDA would outline those issues that prevented an approval. An applicant would have to satisfy each issue in totality and submit a "complete response" to the CR action as a formal amendment which would start a review clock.

Paul inquired whether FDA had a chance to review the responses to the DSI inspection findings for (b) (4). I noted this was still under review.



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

Memorandum

Date: 05/03/11 ESC 05/03/11
From: Erik Laughner, RPM DBOP/ODDP/CDER/FDA
Subject: EUSA Pharma (STN 125359/0); tcon regarding review status of application

EUSA Pharma Attendees:

Tim Corn, MD Chief Medical Officer
Paul Plourde MD Erwinase Project Leader
Bill Bennett VP of Regulatory and QA
Harriette Nadler, Sr Dir Regulatory

FDA Attendees:

Patricia Dinndorf, Suzanne Demko, Patricia Keegan, Erik Laughner, Hong Zhao, Jun Yang,
Charles Bonapace, Michael Skelly

DISCUSSION:

FDA provided EUSA Pharma an update as to the review of the Erwinaze BLA. EUSA Pharma was informed that FDA would not be providing any further requests for amendments for this review cycle and that EUSA Pharma should also provide any unsolicited amendments as they would not be reviewed. FDA would be completing the review and issuing an action letter prior to the PDUFA deadline. Any proposed labeling would be conveyed at the time of this letter. EUSA acknowledged.



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

Memorandum

Date: April 12, 2011
From: Norma Griffin, DBOP/OODP/CDER *NGM 4/12/2011*
Subject: BLA STN 125359 Erwinaze; Standing Monthly Team Meeting

Regulatory Management

Norma Griffin (covering for Erik Laughner)
Patricia Keegan (Director, DBOP)

Clinical

Patricia Dinndorf
Suzanne Demko (CDTL)

Nonclinical

Dubravka Kufirin
Anne Pilaro (TL)

Clinical Pharmacology

Hong Zhao (TL)
Jun Yang

Facilities

Mary Farbman
Anastasia Lolos

Product

Nikolay Spirinidonov
Jacek Cieslak
Serge Beaucage
Susan Kirshner (Immunogenicity)

DBOP Safety Team

Jeff Summers (DDS)
Grace Carmouze (sRPM)

OSE

Sue Kang
Loretta Holmes

Discussion: Participants were present from all disciplines. This monthly standing meeting provided reviewers/teams opportunity to discuss review status of BLA.



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

Memorandum

Date: 04/07/11 *Esc 04/07/11*

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: EUSA Pharma (USA); BLA STN 125359/0; Information Request/Advice re :
DSI findings at PK/PD sample analysis site

From: Laughner, Erik
Sent: Thursday, April 07, 2011 2:37 PM
To: Paul Plourde
Subject: STN 125359; FDA Information Request; Response to DSI findings for (b) (4) Site; (PK/PD analysis)

Dear Paul,

In reference to your call today, you noted the recent tcon between FDA's Division of Scientific Investigations (DSI), EUSA Pharma, and (b) (4). DSI had verbally communicated to you and (b) (4), the specific inspectional findings with respect to the PD and PK assays/results for COG study AALL07P2. You indicated that EUSA Pharma would like to respond to these issues, but requested that they be provided in written format to ensure the verbal issues were fully understood.

The Division provides you these comments in writing which are specific to both the asparaginase and asparagine assays.



040711 DSI
indings IR Memo.d.

We request that EUSA Pharma provide a response back to these findings to the BLA as a formal amendment no later than the end of the month. Please confirm receipt of this email.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

If you have received this message in error, do not use, disclose, reproduce, or distribute this message (including any attachments) and notify me immediately. Thank you.



Memorandum

Date: April 7, 2011
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: FDA Request for Information; BLA STN 125359/0 (Erwinaze); Findings of recent DSI inspection regarding PK/PD sample handling/analysis.

Findings Specific for the Asparaginase Assay:

1. Failure to reject analytical run #480 on 4/8/10 when one of the three quality control (QC) samples failed the acceptance criterion. The following samples were not re-assayed or required dilution:

<u>Subject #</u>	<u>Course #</u>	<u>Sample #</u>
794013	Course #1	PK-01, PK-02
794013	Course #2	PK-01
794013	Course #3	PK-01, PK-03
794165	Course #2	PK-01, PK-03
794669	Course #4	PK-01
794813	Course #1	PK-01 to PK-03, PK-05
794813	Course #1	PK-07, PK-08, PK-012

2. Failure to exclude serum samples from clinical sites received in the thawed state.
3. Records of freezer temperatures for storage of asparaginase samples were not retrievable in an auditable form.
4. Failure to document the times when samples were removed from frozen storage for analysis.
5. Failure to adequately document preparation and storage of asparaginase stock solutions.
6. Failure to adjust nominal asparaginase concentrations in calibrator and quality control solutions for the actual content of L-asparaginase commercial vials.

7. Reported serum asparaginase activities less than the lower limit of quantitation. Specifically, the LLOQ of the asparaginase assay was 0.025 IU/mL. However, asparaginase concentrations ranging from 0.009 to 0.024 IU/mL were reported.

Findings Specific for the Asparagine Assay:

8. Failure to reject analytical runs on 3/9/10, 3/11/10, 3/15/10, 3/25/10, 3/30/10, 4/2/10, 4/8/10, 4/15/10, and 12/8/10 when the quality control (QC) samples failed the acceptance criterion at one or two of the three QC concentrations.
9. Failure to reject chromatograms when no asparagine internal standard was detected or when peaks could not be accurately integrated.
10. Failure to exclude plasma samples from clinical sites which were unacidified or were received in the thawed state.
11. Failure to demonstrate stability of samples under the conditions of the study. Examples:
 - a. The blank plasma used in method development, validation, and QC samples for the asparagine assay was citrate-phosphate-dextrose transfusion plasma, not heparin plasma as in study samples.
 - b. There was no evaluation of freeze/thaw or long-term frozen stability of samples for the asparagine assay. Most plasma samples were stored frozen for 3 to 11 months before assay for asparagine.
 - c. Records of freezer temperatures for storage of asparagine samples were not retrievable in an auditable form. The alarm system for temperatures outside -70°C to -90°C did not record the extreme excursions of temperature and durations of the excursions when the alarm triggered, including the event on 3/4/10 when the majority of study asparagine samples were in this freezer.
 - d. Some samples were received thawed (7 shipments), or without acid preservative for asparagine (61 samples), or with documented delays between sample collection and plasma acidification (multiple examples longer than 10 minutes).

- e. The effectiveness of hydrochloric acid in preserving asparagine in plasma was tested only for *E. coli* asparaginase, not for *Erwinia* asparaginase.
 - f. The times when samples were removed from frozen storage for analysis were not recorded.
12. Between-run accuracy and precision for the asparagine assay were not evaluated.
 13. Failure to evaluate the variability in recovery of asparagine in more than one plasma sample in a run.
 14. Failure to evaluate the stability of asparagine in stock solutions or extracts.
 15. Only a single stock solution of asparagine was used for both calibrators and QC samples, rather than independently-prepared stock solutions, in both pre-study validation and within-study conduct.
 16. Failure to verify (by balance printer or witness) the weights of asparagine used for calibrator and QC stock solutions.



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

Memorandum

Date: 04/07/11 *Esc 04/07/11*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: EUSA Pharma (STN 125359/0); tcon regarding inspections

DISCUSSION:

Dr. Paul Plourde from EUSA Pharma called to acknowledge that DSI had recently (March 25) held a teleconference with ^{(b) (4)} regarding the inspectional findings for his site. Dr. Plourde noted that the teleconference was extensive and that DSI had verbally communicated the various issues identified with regard to both the asparaginase and asparagine assays. Dr. Plourde noted that ^{(b) (4)} noted at the teleconference that in order to respond/rebuff any of the observed deficiencies, he would need the comments in writing. Dr. Plourde noted that FDA should have already been in agreement that the PD assays were never really technically feasible as sample collection at the sites was virtually possible to perform in a way to ensure no sample degradation. With regard to the PK sampling, Dr. Plourde noted that based on the verbal comments, it appeared that only a few samples would have to be omitted from the final analysis. I noted that FDA would hold an internal meeting later next week to review the inspection report as well as the recent inspectional findings for ^{(b) (4)} manufacturing sites which as he was aware also identified issues.

Dr. Plourde noted that formal responses to questions raised from facility and product groups at FDA prior to the inspection would be provided as an amendment within a few days to the BLA. In addition, formal responses to questions raised by the FDA reviewers during the PAI inspection would also be submitted soon to the BLA.



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

Memorandum

Date: March 4, 2011 *EL 03/04/11*
From: Erik Laughner, DBOP/OODP/CDER
Subject: BLA STN 125359 Erwinaze; Fourth Labeling Meeting

Regulatory Management

Erik Laughner
Patricia Keegan (Director, DBOP)

Clinical

Patricia Dinndorf
Suzanne Demko (CDTL)

Discussion: This labeling meeting was convened to discuss the “CONTRAINDICATIONS,” “OVERDOSAGE,” “WARNINGS & PRECAUTIONS,” and “ADVERSE REACTIONS” sections of the proposed package insert label.



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

Memorandum

Date: 03/18/11 ^{EL} 03/18/11
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: EUSA Pharma (USA); BLA STN 125359/0; Information Request/Advice re :
nonclinical protocols

From: Laughner, Erik
Sent: Friday, March 18, 2011 10:17 AM
To: Paul Plourde
Subject: RE: Toxicology Protocols

Hi Paul,

I think these protocols should be formally submitted to the IND rather than the BLA. Yes, please submit now and we will provide an AI letter to the IND.

You can reference the pending BLA in the cover-letter as they relate to the proposed PMR.

Erik

From: Paul Plourde [mailto:Paul.Plourde@eusapharma.com]
Sent: Friday, March 18, 2011 10:05 AM
To: Laughner, Erik
Subject: Toxicology Protocols

Erik,

Here are the proposed toxicology protocols for the Agency's review. We will also submit these as part of an amendment to the BLA or would you rather have us wait until we get the Agency's comments?

Paul

Paul V. Plourde, MD
Senior Vice President
Global Medical Oncology &
US Medical Affairs Head
EUSA Pharma
One Summit Square Suite 201
1717 Langhorne Newtown Road
Langhorne, PA 19047
Phone: 215 867-4923
Fax: 215 579-0384



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

Memorandum

Date: 03/15/11 *ELL 03/15/11*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: EUSA Pharma (USA); BLA STN 125359/0; Information Request/Advice Re :
Proper name.

From: Laughner, Erik
Sent: Tuesday, March 15, 2011 5:44 PM
To: Paul Plourde
Subject: RE: STN 125359 (Erwinaze); Proper Name

Paul,

At this time, FDA will use [REDACTED] ^{(b) (4)} for draft labeling as we revise. Please formally submit the name to USAN for review.

That is all the information we can convey at the moment.
Erik

From: Paul Plourde [mailto:Paul.Plourde@eusapharma.com]
Sent: Thursday, March 10, 2011 9:23 AM
To: Laughner, Erik
Subject: RE: STN 125359 (Erwinaze); Proper Name

Erik

We are happy to accept [REDACTED] ^{(b) (4)} as the proper name. We have contacted USAN and spoken to Ms. Stephanie Shubat who informed us that the FDA recommended name is not likely to be accepted as it they are trying to harmonize the nomenclature. The [REDACTED] ^{(b) (4)} and the INN will be reviewing this name at their April meeting. USAN normally adopts the INN name. Could you advise us on how to proceed.

Paul

Paul V. Plourde, MD
Senior Vice President
Global Medical Oncology &
US Medical Affairs Head
EUSA Pharma
One Summit Square Suite 201
1717 Langhorne Newtown Road
Langhorne, PA 19047
Phone: 215 867-4923

Fax: 215 579-0384

(b) (6)

From: Laughner, Erik [mailto:Erik.Laughner@fda.hhs.gov]
Sent: Tuesday, March 08, 2011 2:59 PM
To: Paul Plourde
Subject: RE: STN 125359 (Erwinaze); Proper Name

Paul,

At this time, FDA would advise that (b) (4) are more acceptable as a proper name and that EUSA Pharma should formally seek USAN approval. Please note that a hyphen should be used in the formal proper name to separate the prefix from the asparaginase.

If you can contact USAN and advise us of the review time for this, we would appreciate.

Please confirm receipt.

Sincerely,

Erik Laughner, RPM

From: Paul Plourde [mailto:Paul.Plourde@eusapharma.com]
Sent: Monday, February 07, 2011 12:08 PM
To: Laughner, Erik
Subject: RE: STN 125359 (Erwinaze); Proper Name

Erik,

Here are nonsensical, non-promotional and devoid of any meaning list for the proper name of Erwinaze. They are listed in order of preference.

Paul

(b) (4)

Paul

Paul V. Plourde, MD
Senior Vice President
Global Medical Oncology &
US Medical Affairs Head
EUSA Pharma
One Summit Square Suite 201
1717 Langhorne Newtown Road
Langhorne, PA 19047
Phone: 215 867-4923
Fax: 215 579-0384

(b) (6)



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

Memorandum

Date: 03/14/11 ^{SSC}
03/14/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: EUSA Pharma (USA); BLA STN 125359/0; Information Request re : ECGs

From: Laughner, Erik
Sent: Monday, March 14, 2011 7:56 AM
To: Paul Plourde
Subject: RE: FDA information Request STN 125359 (Erwinaze); ECG
Importance: High

Paul,

The consult division reviewing the ECG information under STN 125359 has the following information requests:

Please submit the dataset with the required information.

1. QT, QTC (QTCF, QTCB and QTCI if applicable), PR, HR, RR and QRS interval values by each time point for each subject in the QT study.
2. Baseline QT, QTC (QTCF, QTCB and QTCI if applicable), PR, HR, RR and QRS interval values.
3. Change from baseline for QT, QTC (QTCF, QTCB and QTCI if applicable), PR, HR, RR and QRS interval.
4. Please also include time matched concentrations if available.
5. Other standard information like Subject ID, Study ID, Time, Day, Cycle, Treatment and Demographic factors (age, weight, sex etc.) should also be included in the dataset.

All datasets should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file.

Please confirm receipt.

Sincerely,

Erik



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

Memorandum

Date: 03/11/11

EL
03/11/11

From: Erik Laughner, RPM DBOP/ODDP/CDER/FDA

Subject: EUSA Pharma (USA); BLA STN 125359/0; Information Request re : clinical datasets

From: Laughner, Erik
Sent: Friday, March 11, 2011 3:01 PM
To: Paul Plourde
Subject: STN 125359; FDA information request

Paul,

Please see the following clinical information request:

The revised DM.xpt for the EMTP now has 574 subjects, the original DM.xpt had 577. One of the missing subjects is ERW0708. ERW0708 was reported to have grade 3 pancreatitis. Please provide the USUBID (from the original DM.xpt file) for the other 2 missing subjects.

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

If you have received this message in error, do not use, disclose, reproduce, or distribute this message (including any attachments) and notify me immediately. Thank you.



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

Memorandum

Date: 03/10/11
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: EUSA Pharma (USA); BLA STN 125359/0; Information Request/Advice re :
Facilities

From: Laughner, Erik
Sent: Thursday, March 10, 2011 8:56 AM
To: Paul Plourde
Subject: STN 125359; FDA Information Request; Facilities
Importance: High

Paul,

Please see the following attached information requests from our facility group. Please confirm receipt.

Sincerely,

Erik



J31011 CMC DS IR
Memo.doc (77...

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393

erik.laughner@fda.hhs.gov

<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

If you have received this message in error, do not use, disclose, reproduce, or distribute this message (including any attachments) and notify me immediately. Thank you.



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

Memorandum

Date: March 10, 2011
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: FDA Request for Information; BLA STN 125359 (Erwinaze); Product

The following CMC information is being requested for review during the forthcoming pre-approval inspection of Erwinaze manufacturing facilities:



(b) (4)



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

Memorandum

Date: 03/08/11

ESL
03/08/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: EUSA Pharma (USA); BLA STN 125359; Information Request/Advice Re :
Proposed Proper Name

From: Laughner, Erik
Sent: Tuesday, March 08, 2011 2:59 PM
To: 'Paul Plourde'
Subject: RE: STN 125359 (Erwinaze); Proper Name

Paul,

At this time, FDA would advise that [REDACTED] ^{(b)(4)} are more acceptable as a proper name and that EUSA Pharma should formally seek USAN approval. Please note that a hyphen should be used in the formal proper name to separate the prefix from the asparaginase.

If you can contact USAN and advise us of the review time for this, we would appreciate.

Please confirm receipt.

Sincerely,

Erik Laughner, RPM



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

Memorandum

Date: 03/07/11

ESL 03/07/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: EUSA Pharma (STN 125359/0); tcon regarding PDUFA clock

DISCUSSION:

Dr. Paul Plourde from EUSA Pharma called to discuss the 03/04/11 review clock extension letter and to seek clarification as to whether FDA had specific concerns with the CMC portion of the BLA. I noted that the CMC team had previously provided a number of information requests and that additional requests would be provided this week before the team left for inspection in the UK. Dr. Plourde inquired whether the Division had already in fact determined whether the BLA could be approved or not. I clarified that the review clock extension action was deemed necessary to allow review of the extensive CMC information amendment and should not be construed as an indication of not being approved. I noted that while the CMC team did have concerns as noted in the information requests, the team would also need to perform the scheduled inspections as part of the review process.



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

Memorandum

Date: 03/04/11 *EL 03/04/11*

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: EUSA Pharma (STN 125359/0); tcon regarding major amendment

DISCUSSION:

I spoke with Dr. Paul Plourde at EUSA Pharma to inform that FDA had determined that the recent February 23, 2011 CMC amendment was classified by DTP as Major and therefore FDA would extend the PDUFA clock by three months. The new action date would be early August. A formal letter had been drafted and a copy would be provided to Paul via email as a PDF file. Dr. Plourde acknowledged.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125359/0

EXTENSION USER FEE GOAL DATE

March 4, 2011

EUSA Pharma (USA), Inc.
Attention: Paul Plourde, M.D.
Senior Vice President, Global Medical Oncology
One Summit Square, Suite 201
1717 Langhorne Newtown Road
Langhorne, PA 19047

Dear Dr. Plourde:

Please refer to your biologics license application submitted under section 351 of the Public Health Service Act for Erwinaze.

We received your February 23, 2011 amendment to this application on February 23, 2011 and consider it to be a major amendment. Because the receipt date is within three months of the user fee goal date, we are extending the goal date by three months to August 2, 2011, to provide time for a full review of the amendment.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by July 5, 2011.

If you have any questions, contact Erik S. Laughner, Senior Regulatory Health Project Manager, at (301) 796-1393.

Sincerely,

/Patricia Keegan/
Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research



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

Memorandum

Date: March 3, 2011 *SPL 03/3/11*
From: Erik Laughner, DBOP/ODDP/CDER
Subject: BLA STN 125359 Erwinaze; Third Labeling Meeting

Regulatory Management

Erik Laughner
Patricia Keegan (Director, DBOP)

Clinical

Patricia Dinndorf
Suzanne Demko (CDTL)

Clinical Pharmacology

Jun Yang
Hong Zhao

Nonclinical

Dubravka Kufrin
Anne Pilaro (TL)
Leyla Sahin (MHT consult)

Discussion: This labeling meeting was convened to discuss the “CLINICAL PHARMACOLOGY,” “NONCLINICAL TOXICOLOGY,” and “USE IN SPECIAL POPULATIONS” sections of the proposed package insert label.



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

Memorandum

Date: February 23, 2011 *SL 02/23/11*
From: Erik Laughner, DBOP/OODP/CDER
Subject: BLA STN 125359 Erwinaze; Second Labeling Meeting

Regulatory Management

Erik Laughner
Patricia Keegan (Director, DBOP)

Clinical

Patricia Dinndorf
Suzanne Demko (CDTL)

Clinical Pharmacology

Jun Yang
Hong Zhao

Product

Serge Beaucage (TL)
Cristina Ausin
Kim Rains (OBP labeling reviewer)

OSE

Irene Chan
Loretta Holmes

Discussion: This labeling meeting was convened to discuss the “DOSAGE & ADMINISTRATION,” “DOSAGE FORMS & STRENGTHS,” “HOW SUPPLIED/STORAGE AND HANDLING,” and “DESCRIPTION” sections of the proposed package insert label.



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

Memorandum

Date: February 18, 2011 *EL 02/18/11*
From: Erik Laughner, DBOP/OODP/CDER
Subject: BLA STN 125359 Erwinaze; First Labeling Meeting

Regulatory Management

Erik Laughner
Patricia Keegan (Director, DBOP)

Clinical

Patricia Dinndorf
Suzanne Demko (CDTL)

Nonclinical

Dubravka Kufirin
Anne Pilaro (TL)

Clinical Pharmacology

Jun Yang
Hong Zhao

OSE

Irene Chan
Loretta Holmes

Discussion: This labeling meeting was convened to discuss the “INDICATIONS AND USAGE and CLINICAL STUDIES” sections of the proposed package insert label.



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

Memorandum

Date: 02/16/11 ^{ELL}
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: EUSA Pharma (USA); BLA STN 125359/0; Information Request Re : CMC DS

From: Laughner, Erik
Sent: Wednesday, February 16, 2011 2:39 PM
To: 'Paul Plourde'
Subject: STN 125359; FDA Information Request; CMC DS IR
Importance: High

Hello Paul,

Please see the following information requests from our facilities group regarding Drug Substance (DS).



021611 CMC DS IR
Memo.doc (66...

A response by March 4, 2011, is requested.

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

If you have received this message in error, do not use, disclose, reproduce, or distribute this message (including any attachments) and notify me immediately. Thank you.



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

Memorandum

Date: February 16, 2011 {
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: FDA Request for Information; BLA STN 125359 (Erwinaze); CMC; DS

STN 125359 (Erwinaze): CMC Microbiology Drug Substance Information Request:



(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)



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

Memorandum

Date: 02/16/11 *EL*
02/16/11
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: EUSA Pharma (USA); BLA STN 125359/0; Information Request Re : CMC Product



021611 CMC Product
IR Memo.doc

From: Laughner, Erik
Sent: Wednesday, February 16, 2011 3:56 PM
To: Paul Plourde
Subject: STN 125359; FDA Information Request; CMC Product IR
Importance: High

Hello Paul,

Please see the following additional information requests from our CMC group regarding product.

A response by March 4, 2011, is requested.

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

If you have received this message in error, do not use, disclose, reproduce, or distribute this message (including any attachments) and notify me immediately. Thank you.



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

Memorandum

Date: February 16, 2011
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: FDA Request for Information; BLA STN 125359 (Erwinaze); CMC; Product

While conducting the CMC review of STN125359 (Erwinaze), FDA identified the following additional issues:

1. When Erwinaze drug substance (DS) and drug product (DP) were subjected to mechanical stress conditions, you concluded that the appearance test method is vastly superior to SEC-HPLC as a stability-indicating test method. The data supporting this conclusion were supposedly reported in Appendices 1 and 2. However, these appendices could not be found in the BLA submission. Please provide Appendices 1 and 2, which should include the data demonstrating that SEC-HPLC cannot be considered as a stability-indicating test method for Erwinaze DS and DP under mechanical stress conditions.
2. The reconstitution time and appearance analysis of the reconstituted DP are presented in your stability protocol (QCL-70-42-AM-01). However, these DP quality attributes are not monitored through release and stability testing of the DP. Please include reconstitution time and appearance analysis of the DP after reconstitution as release and stability tests. Please submit the proposed specifications and include available test results.
3. Stability testing of the DP at the upper limit of moisture content (b)(4) should be performed throughout the proposed shelf life of the drug product in order to assess whether the quality attributes of the DP are affected by this level of moisture content. The study should include a statistically significant number of vials, each having a moisture content of no less than (b)(4). Please, perform this study or provide a justification and a risk assessment supporting that the study is unnecessary.
4. In order to assess whether the critical quality attributes of the DP are affected within the specified pH range, stability data should be obtained near both the upper and lower limit of the pH specification or the specification should be tightened to reflect either your process capability or your knowledge of the impact pH may have on product quality. Please provide a justification with supporting data for your proposed acceptance criteria.

5. Extended hold times of process intermediates have the potential to affect the quality attributes of the drug product. Please validate hold times for each drug product process intermediate, where applicable, in order to demonstrate that drug product quality is not affected by these hold times. This study should include a worst case hold scenario defined by the cumulative maximal time for each hold step along with an evaluation of the purity and potency of process intermediates and of the resulting drug product. Please submit the available validation data for review and your plans for fully validating hold times.
6. Please be advised that the General Safety Test (GST) is a regulatory requirement (21 CFR § 610.11) for a non-specified biological product. We believe your product may qualify for an exemption as described under 610.11 (g) (2) but you need to submit your justification as to why this test is unnecessary in your BLA. Please submit a request for an exemption from the GST along with your justification to the BLA.
7. In regard to manufacturing process controls:





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

Memorandum

Date: February 15, 2011
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: BLA STN 125359 Erwinaze; Standing Monthly Team Meeting

EKL
02/15/11

Regulatory Management

Erik Laughner
Patricia Keegan (Director, DBOP)

Clinical

Patricia Dinndorf
Suzanne Demko (CDTL)

Nonclinical

Dubravka Kufirin
Anne Pilaro (TL)

Facilities

Mary Farbman
Patricia Hughes (TL)

Product

Cristina Ausin
Serge Beaucage
Susan Kirshner (Immunogenicity)

DBOP Safety Team

Jeff Summers (DDS)
Grace Carmouze (sRPM)

OSE

Sue Kang

Discussion: Participants were present from most disciplines. This monthly standing meeting provided reviewers/teams opportunity to discuss review status of BLA.



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

Memorandum

Date: February 11, 2011 *ESL 02/11/11*
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: BLA STN 125359 Erwinaze; Mid-Cycle Meeting

A mid-cycle meeting was held. Participants were present from all disciplines. The following disciplines gave slide presentations to OODP:

- Erik Laughner, RPM
- Jacek Cieslak, CMC
- Anastasia Lolas, Facility
- Dubraka Kufirin, Nonclinical
- Patricia Dinndorf, Clinical
- Jun Yang, Clinical Pharmacology



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

Memorandum

Date: 2/01/11 234
2/1/11
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: EUSA Pharma (USA); BLA STN 125359/0; Information Request re : clinical datasets

From: Laughner, Erik
Sent: Tuesday, February 01, 2011 4:19 PM
To: Paul Plourde
Subject: FW: FDA Information Request; STN 125359 (Erwinaze)

Paul,

Please see the following responses:

1. Your reason for not including 798213 in the Safety Population is noted.
2. Patient CRFs "Adverse Events CRF" Third column "CTC AE v 3.0 AE Type" lists codes such as 5128077 or 5119000. I am looking for an index that defines what AEs these codes signify.

Please confirm receipt.

Sincerely,

Erik

From: Paul Plourde [mailto:Paul.Plourde@eusapharma.com]
Sent: Tuesday, February 01, 2011 10:55 AM
To: Laughner, Erik
Subject: RE: FDA Information Request; STN 125359 (Erwinaze)

Our Team is preparing a response to your questions received in your January 28th email but need some clarification on two of the questions. We hope to have all of the responses to those questions by February 7th.

FDA Question:798213: This patient received 2 doses of Erwinaze and had an allergic reaction. Adverse event report was filed which documents these doses. Should be part of the safety population.

The explanation for this patient was provided in BLA Amendment 005 submitted on January 14, 2012. Since this patient's AE was discovered after the data cut off of April 30, 2010 it should not

be included in the data base. The narrative written in the CSR does have the AE which was included in error. Obviously this AE and narrative would be included in the final report. Do you still want this AE in the database even if it was after the cut-off date? I have pasted the response in the Amendment 005 on this patient for convenience.

The Dosing Spreadsheet was generated from the Specimen Transfer Forms which accompanied blood specimens to the (b) (4). While patient #798213 was enrolled into the trial, blood samples were never forwarded from the site to the laboratory. For this reason, there were no specimen transfer sheets generated for this patient and in turn this patient was not included on the Dosing Spreadsheet. The site has been contacted and reports that once the patient was removed from the study after Dose 2 of Course 1, they felt that there was no need to submit the blood samples despite the fact that they are required to do so per protocol. Patient 798213 was removed from the study post dose 2 occurring on 4/30/2010.

The Sponsor did not become aware of the AE for patient 798213 until 5 May. The data cut-off for the ALL07P2 study was 30 April. Therefore, the narrative for patient 798213 was included in error and remains as part of the submission for completeness.

In the process of investigating patient 798213, it was discovered that this patient was inadvertently included in some listings that the patient should not have been part of. As a result, the listings in Appendix 1 to Appendix 5 have been updated and replace the previous listings.

EUSA

FDA Question: Clarify if the BLA application includes a guide that maps AE to the AE code used on the COG CRF. If so, please tell FDA where to locate it. If not provided, please submit as soon as possible.

Could you clarify as we are not sure what is being requested? The AEs were collected via electronic forms that had a drop down box. The investigators had only those options in capturing the AE and that information is considered to the source verbatim term. There was no free text for the investigator to write and again the only options were what was in the drop down boxes. In Amendment 004, December 31st, 2010 we provided the entire mapping of the COG verbatim term and the MedDRA hierarchy. We are uncertain as to what the AE code on the COG CRF you are referencing? To our knowledge there was no AE code on the electronic form.

Paul

Paul V. Plourde, MD
Senior Vice President
Global Medical Oncology &
US Medical Affairs Head
EUSA Pharma
One Summit Square Suite 201
1717 Langhorne Newtown Road
Langhorne, PA 19047
Phone: 215 867-4923
Fax: 215 579-0384

(b) (6)

From: Laughner, Erik [mailto:Erik.Laughner@fda.hhs.gov]
Sent: Friday, January 28, 2011 9:06 AM
To: Paul Plourde
Subject: FDA Information Request; STN 125359 (Erwinaze)
Importance: High

Hello Paul,

Clinical has the following information requests:

Page 49/145 of the Study Report states "Patient 791653 is not eligible and Patient 798213 appears to not to have been dosed." See specific questions about these patients below.

FDA queries for the following patient IDs:

791653: Why is this patient characterized as ineligible? This patient should be eligible based on the answers to questions 16.2.3.2 page 3/5 and 16.2.3.4 page 3/5. A PK worksheet indicates patient received Erwinaze.

798213: This patient received 2 doses of Erwinaze and had an allergic reaction. Adverse event report was filed which documents these doses. Should be part of the safety population.

797513: This patient was categorized as not eligible; see 16.2.3.2 page 4/5 and 16.2.3.4 page 4/5. This patient was not eligible because he was not eligible for the primary treatment protocol. He appeared to receive 1 dose of Erwinaze prior to determination he was not eligible. Therefore he should not be included in the evaluable population nor in the safety population.

Clarify why patients 787929 and 792125 were not included in the evaluable population.

Clarify why patient 795925 was evaluable for PD but not PK.

Clarify if the BLA application includes a guide that maps AE to the AE code used on the COG CRF. If so, please tell FDA where to locate it. If not provided, please submit as soon as possible.

Clarify why were PK evaluations but not PD evaluations available for the following 7 subjects: 789794, 791449, 792906, 793635, 794966, 796268, 798278

Please confirm receipt.

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

If you have received this message in error, do not use, disclose, reproduce, or distribute this message (including any attachments) and notify me immediately. Thank you.



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

Memorandum

Date: 1/28/11

242
01/28/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: EUSA Pharma (USA); BLA STN 125359/0; Information Request re : clinical datasets

From: Laughner, Erik [mailto:Erik.Laughner@fda.hhs.gov]
Sent: Friday, January 28, 2011 9:06 AM
To: Paul Plourde
Subject: FDA Information Request; STN 125359 (Erwinaze)
Importance: High

Hello Paul,

Clinical has the following information requests:

Page 49/145 of the Study Report states "Patient 791653 is not eligible and Patient 798213 appears to not to have been dosed." See specific questions about these patients below.

FDA queries for the following patient IDs:

791653: Why is this patient characterized as ineligible? This patient should be eligible based on the answers to questions 16.2.3.2 page 3/5 and 16.2.3.4 page 3/5. A PK worksheet indicates patient received Erwinaze.

798213: This patient received 2 doses of Erwinaze and had an allergic reaction. Adverse event report was filed which documents these doses. Should be part of the safety population.

797513: This patient was categorized as not eligible; see 16.2.3.2 page 4/5 and 16.2.3.4 page 4/5. This patient was not eligible because he was not eligible for the primary treatment protocol. He appeared to receive 1 dose of Erwinaze prior to determination he was not eligible. Therefore he should not be included in the evaluable population nor in the safety population.

Clarify why patients 787929 and 792125 were not included in the evaluable population.

Clarify why patient 795925 was evaluable for PD but not PK.

Clarify if the BLA application includes a guide that maps AE to the AE code used on the COG CRF. If so, please tell FDA where to locate it. If not provided, please submit as soon as possible.

Clarify why were PK evaluations but not PD evaluations available for the following 7 subjects: 789794, 791449, 792906, 793635, 794966, 796268, 798278

Please confirm receipt.

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393

erik.laughner@fda.hhs.gov

<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

If you have received this message in error, do not use, disclose, reproduce, or distribute this message (including any attachments) and notify me immediately. Thank you.



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

Memorandum

Date: 1/28/11 ^{ESL} 1/28/11
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: EUSA Pharma (USA); BLA STN 125359/0; Information request/advice re :
Proposed Proper Name

From: Laughner, Erik
Sent: Friday, January 28, 2011 2:44 PM
To: 'Paul Plourde'
Subject: RE: STN 125359 (Erwinaze); Proper Name

Hello Paul,

CDER has made the determination that the suggested prefixes are not nonsensical, nonpromotional, and devoid of meaning, as was recommended.

In the simplest terms, you need to come up with 2 new prefixes that are totally devoid of meaning (ie. nonsensical and nonpromotional).

If you can provide these new suggestions next week, we will have reviewed.

Please confirm receipt.

Sincerely,

Erik Laughner, RPM

From: Paul Plourde [mailto:Paul.Plourde@eusapharma.com]
Sent: Monday, December 13, 2010 12:01 PM
To: Laughner, Erik
Subject: RE: STN 125359 (Erwinaze); Proper Name

Below you will find a some suggested proper names for Erwinaze. We would favor (b) (4)
(b) (4) As pediatric trials in ALL are becoming more global,
this would make it more identifiable to the investigators. Here are our suggested names:

(b) (4)

Regards,

Paul

Paul V. Plourde, MD
Senior Vice President
Global Medical Oncology &
US Medical Affairs Head
EUSA Pharma
One Summit Square Suite 201
1717 Langhorne Newtown Road
Langhorne, PA 19047
Phone: 215 867-4923
Fax: 215 579-0384

(b) (6)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125359/0

FILING ISSUES

January 14, 2011

EUSA Pharma (USA), Inc.
Attention: Paul Plourde, M.D.
Senior Vice President, Global Medical Oncology
One Summit Square, Suite 201
1717 Langhorne Newtown Road
Langhorne, PA 19047

Dear Dr. Plourde:

Please refer to your complete biologics license application (BLA) received November 1, 2010, submitted under section 351 of the Public Health Service Act for Erwinaze. Also refer to our filing letter dated December 28, 2010. While conducting our filing review we identified the following potential review issues:

Product

1. In regard to Erwinaze drug substance (DS) manufacturing process and process control:



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

Product-Microbiology

8. The rabbit pyrogen test should be conducted at least once to demonstrate that your biologic product does not contain pyrogenic substances other than bacterial endotoxins. Please provide information and summary data for the rabbit pyrogen test of Erwinaze (L-asparaginase) in conformance to 21CFR610.13(b) using product manufactured with the proposed commercial manufacturing process.

Product-Immunoassays

9. As discussed during the December 17, 2010, teleconference, the proposed immunoassays are not yet validated to allow for use with clinical trial samples. We acknowledge that you have committed to provide a plan to your IND by the week of January 20th which describes the timeframe to re-develop and validate the assays. We will consider the final developmental, validation of these assays, and screening of archived patient serum samples as a postmarketing requirement (PMR) for an eventual approval of Erwinaze.

Nonclinical

10. The electronic scanned copies of the nonclinical study reports (Study numbers (b) (4) -DPH-71-02 (first page only), (b) (4) -DPH-69-00, (b) (4) -DPH- 71-01) are not legible. Please provide paper copies of these study reports, and ensure that all critical information including dosing, clinical and histopathology findings and any available toxicokinetic data are clearly presented and legible, to facilitate review.
11. Please provide your plans and a timeline for a conduct of developmental and reproductive toxicity studies as a postmarketing requirement.

Clinical

12. For the Erwinase Master Treatment Protocol (EMTP) data provided in the BLA, we performed an audit of the safety data submitted to determine the quality of this data. CRFs of 122 subjects of the 577 were reviewed and compared to the safety data captured in the ADAE.xpt. (Initially 44 subjects were audited but problems were identified in 12 cases and the audit was expanded to more fully ascertain the extent of the problems.) Subjects who received their first dose of *Erwinia* asparaginase in the months of May, August, and November were reviewed. The following problems were identified:
 - a. There were no CRFs for 16 of 122 subjects selected for this audit:
[EMTP-000000099999064, ERW0355, EMTP-000000099999072, ERW0704, ERW0126, EMTP-000000099999055, EMTP-000000099999057, EMTP-

000000099999070, EMTP-000000099999074, ERW0328, ERW0707, EMTP-000000000000NA, EMTP-000000100062136, EMTP-001709449669039, ERW0543, ERW0712]

- b. There were 12 subjects without reported adverse events with adverse event identified on the CRFs: [EMTP-000000001647819 - Grade 1 AST ALT, EMTP-000000099999063 - Grade 1 AST ALT, EMTP-000000000781776 - Grade 1 Systemic allergic reaction, EMTP-00000Z000936864 - Systemic allergic reaction, EMTP-000000018839126 - Grade 4 anaphylactic reaction, EMTP-000000011052351 - Grade 1 Systemic allergic reaction, EMTP-000000000418614 - Thrombotic event "DVT of R subclavian vein near portacath" abn Prot C and ATIII documented; AE report submitted called allergic more likely thrombotic, EMTP-000000000787175 - Grade 4 elevated ALT, EMTP-000000001673684 - Grade 1 systemic allergic reaction, EMTP-000000002439734 - Local reaction, EMTP-000000008803398 - Grade 3 hyperglycemia, EMTP-000000015925523 - Grade 2 systemic allergic reaction]
- c. There were 3 subjects with adverse events (AEs) reported although no AEs were documented on the case report forms (CRFs); [EMTP-000000001059067 (Date of AEs (4/18/08) prior to date of erwinaze administration (5/12/09)), EMTP-000000000507957, EMTP-000000001156674]
- d. The CRFs were designed as check box queries. The verbatim term generated "AETERM" and the MedDRA term it was mapped to "AECODE" should have been consistent each time an adverse event was identified from a check box from the form, i.e., each check box should have had a designated MedDRA term assigned to it. This was not the case. For example:
- In the case of allergic reaction, if "Local Reaction" was checked it was reported as "AETERM" - "skin reaction", "AECODE" - "skin reaction" for Subject EMTP-000000000025579; "urticaria" for Subject EMTP-000000006687270; and "hypersensitivity" for Subject EMTP-000000099999082.
 - Systemic Allergic reaction grade 1 was coded as "anaphylactic reaction" for Subjects EMTP-000000000779117, and EMTP-000000000790100; "hypersensitivity" for Subject EMTP-000000001413127.
 - Systemic Allergic reaction grade 2 was coded as "anaphylactic reaction" for Subjects EMTP-000000099999048; and hypersensitivity" for Subject EMTP-000000000747797.
 - Systemic Allergic reaction grade 3 was coded as "eyelid edema", for Subject EMTP-000000000004978; "hypotension" for Subject EMTP-000000001249691.

Revise the AE.xpt and ADAE.xpt datasets for the EMTP. Include the full MedDRA hierarchy for each event. For AEs identified from a checkbox item choose a consistent verbatim term and map it to a consistent preferred term. Use the NCI CTCAE version 3 for grading throughout. Please use the suggested approach that was provided to you in some detail via electronic email (email) by this Division on January 6, 2011.

13. Provide a list of all patients enrolled under the EMTP study for whom there are no CRFs available.
14. Confirm that between February 2006 and April 19, 2010, Erwinaze was only distributed to 577 individuals in the US. Confirm that 569 sets of data capture forms were returned.
15. Include all Adverse Drug Event reports submitted on these patients in their CRFs.
16. Regarding clinical trial ALLO7P2 provided in the BLA:
 - a. If a patient had an Adverse Drug Event report filed, include the report in the CRF.
 - b. Include the "COG electronic case report form" in the CRFs. This form was identified as being associated with discrepancies in the December 31, 2010 submission in section 1.6.3 "Correspondence Regarding Meetings – 0004" on page 9 of 25. "COG electronic case report forms that included the data that was not consistent with the spreadsheet provided by (b) (4)
17. The integrated summary of safety (ISS) dataset for both the revised AALL07P2 and EMTP datasets should be mapped to the full MedDRA hierarchy consistent with the associated AE and ADAE datasets to fully update the ISS dataset.

Proposed Labeling

18. We have completed a preliminary review of the proposed labeling submitted in this application and provide, as an attachment to this letter, a preliminary revision that contains comments based on 21 CFR Parts 201.56 and 201.57, the preamble to the Final Rule, and FDA Guidance documents. Please address the identified deficiencies/issues and re-submit labeling in clean and red-line MS WORD versions as an amendment to your application by February 28, 2011. This revised labeling will be used for further labeling discussions.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application. Following a review of the application, we will advise you in writing of any action we have taken and request additional information if needed.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, contact Erik S. Laughner, Senior Regulatory Health Project Manager, at (301) 796-1393.

Sincerely,

/Patricia Keegan/

Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research

Enclosure: FDA preliminary labeling comments

14 PAGES OF DRAFT LABELING HAVE BEEN WITHHELD IN FULL AS b4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE



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

Memorandum

Date: 1/12/11 *ESL 01/12/11*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: EUSA Pharma (USA); BLA STN 125359/0; FDA information requests re:
clinical datasets

From: Laughner, Erik
Sent: Wednesday, January 12, 2011 4:15 PM
To: Paul Plourde
Subject: STN 125359; FDA Information Request

Hello Paul,

We have the following clinical information requests:

Please confirm:

FA.xpt is the dataset that contains the information describing the previous reaction to *E coli* asparaginase that resulted in the need to treat the patient with Erwinaze.

This information is identified in rows of data identified in the FACAT column as "Previous treatment with L-Asparaginase." The items in the FAOBJ column are the adverse reactions that precluded further therapy with *E. coli* asparaginase and those that were checked on the CRF are designated by Y in the FAORRES column.

In FA.xpt in rows identified in the FACAT column as "Previous treatment with L-Asparaginase" what is the difference between subjects with the designation "Pegylated" and "Pegaspargase" in the FATEST column?

Where can I find the subject IDs for the 8 subjects who did not receive Erwinaze [not in the "Safety Population"]?

Is there a dataset with a column that indicates that the patient did receive Erwinaze and therefore that patient is included in the "Safety Population" [received at least one dose of Erwinaze]? If not this should be part of the DM.xpt dataset. When the DM.xpt dataset is being revised please add this information as ARM column and categorize subjects as either "Safety Population" or "Not treated."

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393

erik.laughner@fda.hhs.gov

<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

If you have received this message in error, do not use, disclose, reproduce, or distribute this message (including any attachments) and notify me immediately. Thank you.



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

Memorandum

Date: January 7, 2011 *ESL 01/07/11*
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: BLA STN 125359 Erwinaze; Standing Monthly Team Meeting

Regulatory Management

Erik Laughner
Patricia Keegan (Director, DBOP)

Clinical

Suzanne Demko (CDTL)
Patricia Dinndorf

Nonclinical

Dubravka Kufrin
Anne Pilaro (TL)

Clinical Pharmacology

Jun Yang
Hong Zhao (TL)

Facilities

Mary Farbman
Patricia Hughes (TL)

Product

Jacek Cieslak
Nikolay Spiridonov
Serge Beaucage
Susan Kirshner (Immunogenicity)

DBOP Safety Team

Jeff Summers (DDS)
Grace Carmouze (sRPM)

Discussion: Participants were present from all disciplines. This monthly standing meeting provided reviewers/teams opportunity to discuss review status of BLA.



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

Memorandum

Date: 1/6/11 *EL 01/06/11*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: EUSA Pharma (USA); BLA STN 125359/0; FDA information request/advice
re: application deficiencies

From: Laughner, Erik
Sent: Thursday, January 06, 2011 8:59 AM
To: Paul Plourde
Subject: FDA information Request STN 125359 (Erwinaze); Clinical
Importance: High

Paul,

We will be sending a 74-day letter next week. The following information request will be outlined in the that letter; however, we also provide it now to expedite.

Please confirm receipt.

Sincerely,

Erik



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

Memorandum

Date: January 6, 2011
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: FDA Request for Information; BLA STN 125359 (Erwinaze)

For EMTP

An audit of the safety data submitted from the EMTP was performed to determine the quality of this data. CRFs of 122 subjects of the 577 were reviewed and compared to the safety data captured in the ADAE.xpt. (Initially 44 subjects were audited but problems were identified in 12 cases and the audit was expanded to more fully ascertain the extent of the problems.) Subjects who received their first dose of *Erwinia* asparaginase in the months of May, August, and November were reviewed. The following problems were identified:

- There were no CRFs for 16 of 122 subjects selected for this audit.
[EMTP-000000099999064, ERW0355, EMTP-000000099999072, ERW0704, ERW0126, EMTP-000000099999055, EMTP-000000099999057, EMTP-000000099999070, EMTP-000000099999074, ERW0328, ERW0707, EMTP-000000000000NA, EMTP-000000100062136, EMTP-001709449669039, ERW0543, ERW0712]
- There were 12 subjects without reported adverse events with adverse event identified on the CRFs.
[EMTP-000000001647819 - Grade 1 AST ALT, EMTP-000000099999063 - Grade 1 AST ALT, EMTP-000000000781776 - Grade 1 Systemic allergic reaction, EMTP-00000Z000936864 - Systemic allergic reaction, EMTP-000000018839126 - Grade 4 anaphylactic reaction, EMTP-000000011052351 - Grade 1 Systemic allergic reaction, EMTP-000000000418614 - Thrombotic event "DVT of R subclavian vein near portacath" abn Prot C and ATIII documented; AE report submitted called allergic more likely thrombotic, EMTP-000000000787175 - Grade 4 elevated ALT, EMTP-000000001673684 - Grade 1 systemic allergic reaction, EMTP-000000002439734 - Local reaction, EMTP-000000008803398 - Grade 3 hyperglycemia, EMTP-000000015925523 - Grade 2 systemic allergic reaction]
- There were 3 subjects with AEs reported although no AEs were documented on the CRFs.
[EMTP-000000001059067 (Date of AEs (4/18/08) prior to date of erwinaze administration (5/12/09)), EMTP-000000000507957, EMTP-000000001156674]

- The CRFs were designed as check box queries. The verbatim term generated “AETERM” and the MedDRA term it was mapped to “AECODE” should have been consistent each time an adverse event was identified from a check box from the form, i.e., each check box should have had a designated MedDRA term assigned to it. This was not the case.

For example, in the case of allergic reaction, if “Local Reaction” was checked it was reported as “AETERM” - “skin reaction”, “AECODE” – “skin reaction” for Subject EMTP-00000000025579; “urticaria” for Subject EMTP-00000006687270; and “hypersensitivity” for Subject EMTP-000000099999082.

Systemic Allergic reaction grade 1 was coded as “anaphylactic reaction” for Subjects EMTP-00000000779117, and EMTP-00000000790100; “hypersensitivity” for Subject EMTP-00000001413127.

Systemic Allergic reaction grade 2 was coded as “anaphylactic reaction” for Subjects EMTP-000000099999048; and hypersensitivity” for Subject EMTP-00000000747797.

Systemic Allergic reaction grade 3 was coded as “eyelid edema”, for Subject EMTP-00000000004978; “hypotension” for Subject EMTP-000000001249691.

1. Revise the AE.xpt and ADAE.xpt datasets for the EMTP. Include the full MedDRA hierarchy for each event. For AEs identified from a checkbox item choose a consistent verbatim term and map it to a consistent preferred term. Use the NCI CTCAE version 3 for grading throughout. Please use the suggested approach for coding or justify an alternative.

COPYRIGHT MATERIAL

If "Allergic reaction" is identified as yes and only Local reaction is checked. This should be coded as below.

Verbatim	Preferred Term	SOC
"Local reaction"	"Local Reaction"	General disorders and administration site disorders

Note, in some cases only "Local reaction" was checked but there is further description that indicates this was a hive at a distant site. In this case this should be coded as a "Grade 2 Systemic allergic reaction."

If "Systemic reaction" is checked the data should be coded as follows:

Verbatim	Preferred Term	SOC
"Grade 1 Systemic allergic reaction"	"Hypersensitivity"	Immune System Disorders
"Grade 2 Systemic allergic reaction"	"Hypersensitivity"	Immune System Disorders
"Grade 3 Systemic allergic reaction"	"Hypersensitivity"	Immune System Disorders
"Grade 4 Systemic allergic reaction"	"Hypersensitivity"	Immune System Disorders
"Grade 5 Systemic allergic reaction"	"Hypersensitivity"	Immune System Disorders

If "Systemic reaction was not checked but urticaria or hives are reported on the CRF code this as "Grade 2 Systemic allergic reaction."

COPYRIGHT MATERIAL

If further description of the event is provided, include that information. Such as "CNS hemorrhage" the following should be coded.

Verbatim	Preferred Term	SOC
"Cerebral hemorrhage"	"Cerebral haemorrhage"	Nervous System Disorders

COPYRIGHT MATERIAL

If abnormal laboratory values are documented they should be graded using the CTCAE grading system and coded as follows:

Verbatim	Preferred Term	SOC
"Grade 1 PT"	"Prothrombin time prolonged"	Investigations
"Grade 2 PT"	"Prothrombin time prolonged"	Investigations
"Grade 3 PT"	"Prothrombin time prolonged"	Investigations

"Grade 1 PTT"	"Activated partial thromboplastin time prolonged"	Investigations
"Grade 2 PTT"	"Activated partial thromboplastin time prolonged"	Investigations
"Grade 3 PTT"	"Activated partial thromboplastin time prolonged"	Investigations

"Grade 1 Fibrinogen"	"Blood fibrinogen decreased"	Investigations
"Grade 2 Fibrinogen"	"Blood fibrinogen decreased"	Investigations
"Grade 3 Fibrinogen"	"Blood fibrinogen decreased"	Investigations
"Grade 4 Fibrinogen"	"Blood fibrinogen decreased"	Investigations

There is no CTCAE grading for protein C, protein S, or AT III. These should be coded as follows:

Verbatim	Preferred Term	SOC
"Protein C decreased"	"Protein C decreased"	Investigations
"Protein S decreased"	"Protein S decreased"	Investigations
"AT III decreased"	"Antithrombin III decreased"	Investigations

COPYRIGHT MATERIAL

If "Hepatobiliary/ pancreas disorders is checked the data should be coded based on the category chosen from the table.

Verbatim	Preferred Term	SOC
"Grade 2 Liver disorder"	"Liver disorder"	Hepatobiliary Disorders
"Grade 3 Liver disorder"	"Liver disorder"	Hepatobiliary Disorders
"Grade 4 Liver disorder"	"Liver disorder"	Hepatobiliary Disorders
"Grade 5 Liver disorder"	"Liver disorder"	Hepatobiliary Disorders
"Grade 1 Pancreatitis"	"Pancreatitis"	Gastrointestinal Disorders
"Grade 2 Pancreatitis"	"Pancreatitis"	Gastrointestinal Disorders
"Grade 3 Pancreatitis"	"Pancreatitis"	Gastrointestinal Disorders
"Grade 4 Pancreatitis"	"Pancreatitis"	Gastrointestinal Disorders
"Grade 5 Pancreatitis"	"Pancreatitis"	Gastrointestinal Disorders

COPYRIGHT MATERIAL

If abnormal laboratory values are documented they should be graded using the CTCAE grading system and coded as follows:

Verbatim	Preferred Term	SOC
"Grade 1 AST"	"Aspartate aminotransferase increased"	Investigations
"Grade 2 AST"	"Aspartate aminotransferase increased"	Investigations
"Grade 3 AST"	"Aspartate aminotransferase increased"	Investigations
"Grade 4 AST"	"Aspartate aminotransferase increased"	Investigations
"Grade 1 ALT"	"Alanine aminotransferase increased"	Investigations
"Grade 2 ALT"	"Alanine aminotransferase increased"	Investigations
"Grade 3 ALT"	"Alanine aminotransferase increased"	Investigations
"Grade 4 ALT"	"Alanine aminotransferase increased"	Investigations
"Grade 1 Bilirubin"	"Blood bilirubin increased"	Investigations
"Grade 2 Bilirubin"	"Blood bilirubin increased"	Investigations
"Grade 3 Bilirubin"	"Blood bilirubin increased"	Investigations
"Grade 4 Bilirubin"	"Blood bilirubin increased"	Investigations
"Grade 1 Amylase"	"Blood amylase increased"	Investigations
"Grade 2 Amylase"	"Blood amylase increased"	Investigations
"Grade 3 Amylase"	"Blood amylase increased"	Investigations
"Grade 4 Amylase"	"Blood amylase increased"	Investigations
"Grade 1 Lipase"	"Lipase increased"	Investigations
"Grade 2 Lipase"	"Lipase increased"	Investigations
"Grade 3 Lipase"	"Lipase increased"	Investigations
"Grade 4 Lipase"	"Lipase increased"	Investigations

COPYRIGHT MATERIAL

Verbatim	Preferred Term	SOC
"Grade 3 Hyperglycemia"	"Hyperglycaemia"	Investigations
"Grade 4 Hyperglycemia"	"Hyperglycaemia"	Investigations
"Grade 5 Hyperglycemia"	"Hyperglycaemia"	Investigations

Any information captured in this section should be captured as verbatim terms and coded in MedDRA.

In addition to systematically revising the AE.xpt and ADAE.xpt datasets for the EMTP please respond to the following items.

2. Provide a list of all EMTP patients for whom there are no CRFs available.
3. Confirm that between Feb 2006 and April 19, 2010 Erwinaze was only distributed to 577 individuals in the US. Confirm that 569 sets of data capture forms were returned.
4. Include all Adverse Drug Event reports submitted on these patients in their CRFs.

For ALL07P2

1. For the AALL07P2 if patient had an Adverse Drug Event report filed include the report in the CRF.
2. Include the “COG electronic case report form” in the CRFs. This form was identified as being associated with discrepancies in the December 31, 2010 submission in section 1.6.3 “Correspondence Regarding Meetings – 0004” on page 9 of 25. “COG electronic case report forms that included the data that was not consistent with the spreadsheet provided by (b) (4).”

For ISS

1. Update the ISS datasets with the revisions made to the AALL07P2 datasets and the EMTP datasets. Add the full MedDRA hierarchy to the AE and ADAE datasets for the ISS datasets.



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

Memorandum

Date: 01/03/11 *la 01/03/11*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: EUSA Pharma (USA); BLA STN 125359/0; FDA information request re:
ECGs

From: Laughner, Erik
Sent: Monday, January 03, 2011 9:26 AM
To: 'Paul Plourde'
Subject: FDA information Request STN 125359 (Erwinaze); ECG
Importance: High

Hello Paul and Happy New Year,

An internal consult has been generated to review the QT data from Clinical Study Report AALL07P2 submitted in the BLA. The reviewing group has requested that the following table be filled out and returned as soon as possible. In addition please submit all related ECG waveforms to the ECG warehouse at www.ecgwarehouse.com



HighlightsofClinicalP
harmacolo...

Please confirm receipt.

Sincerely,

Erik Laughner, RPM

Highlights of Clinical Pharmacology STN 125359 (ERWINAZE)

Therapeutic dose	Include maximum proposed clinical dosing regimen.	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) C _{max} and AUC
	Multiple Dose	Mean (%CV) C _{max} and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	T _{max}	<ul style="list-style-type: none"> • Median (range) for parent • Median (range) for metabolites
Distribution	V _d /F or V _d	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated • Other routes
	Terminal t _{1/2}	<ul style="list-style-type: none"> • Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in C _{max} and AUC
	Sex	Specify mean changes in C _{max} and AUC
	Race	Specify mean changes in C _{max} and AUC
	Hepatic & Renal Impairment	Specify mean changes in C _{max} and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in C _{max} and AUC
	Food Effects	Specify mean changes in C _{max} and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical	Describe worst case scenario and expected fold-change in C _{max} and	

Exposure Scenario	AUC. The increase in exposure should be covered by the supra-therapeutic dose.
--------------------------	--



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125359/0

FILING COMMUNICATION
December 28, 2010

EUSA Pharma (USA), Inc.
Attention: Paul Plourde, M.D.
Senior Vice President, Global Medical Oncology
One Summit Square, Suite 201
1717 Langhorne Newtown Road
Langhorne, PA 19047

Dear Dr. Plourde:

This letter is in regard to your biologics license application (BLA), submitted under section 351 of the Public Health Service Act, for Erwinaze.

We have completed an initial review of your application to determine its acceptability for filing. Under 21 CFR 601.2(a), we have filed your application today. The review classification for this application is Priority. Therefore, the user fee goal date is May 3, 2011. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

While conducting our filing review, we identified potential review issues and will be communicating them to you on or before January 14, 2011.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by April 5, 2011.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, contact Erik S. Laughner, Senior Regulatory Health Project Manager, at (301) 796-1393.

Sincerely,

/Jeff Summers/

Jeff Summers, M.D., on behalf of Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research



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

Memorandum

Date: 12/21/10 *ESC 12/21/10*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: EUSA Pharma (STN 125359/0); tcon regarding clinical dataset issues

FDA ATTENDEES:

Erik Laughner, RPM
 Suzanne Demko, Clinical Team Leader
 Jeff Summers, Deputy Director of Safety

EUSA PHARMA ATTENDEES:

EUSA

Tim Corn, MD	CMO
Harriette Nadler	Sr Dir Regulatory
	(b) (4)
Taheri Mercedes MD	Pharmacovigilance, US
Emma Bolton	Pharmacovigilance, UK

(b) (4)

BACKGROUND:

In follow-up to the 12/16/10 tcon discussing pre-filing clinical deficiencies, FDA requested an additional tcon. Prior to the call, on 12/20, EUSA Pharma provided FDA via email, documents for review (see attached at end of this tcon record).

DISCUSSION/ACTION ITEMS:

FDA acknowledged the receipt and review of EUSA Pharma's email and attachments. The following is a high-level summary of the tcon:

- EUSA Pharma acknowledged the incorrect coding of the AE data set in the column labeled AEBODYYS designated as "uncoded". These were duplicates and would be corrected. EUSA pharma also agreed to formally provide a written explanation of the source of the issues identified with the EX.xpt data set.
- EUSA Pharma agreed to provide an updated data set containing all AEs with the verbatim term and full MedDRA coding.
- EUSA Pharma agreed that All Specimen Transfer CRFs will be provided for all courses.
- EUSA Pharma agreed to provide EX.xpt data set which contains the actual administered dose.

All the above information would be provided as a formal amendment to the BLA by December 31, 2010.

FDA also requested that ADEER reports be provided. The AE should be hyperlinked to the datasets or CRFs. EUSA agreed to provide this information but it would take more time. FDA acknowledged a target submission date of January 15, 2011.

From: Paul Plourde [mailto:Paul.Plourde@eusapharma.com]
Sent: Monday, December 20, 2010 11:04 AM
To: Laughner, Erik
Subject: Tomorrow's call

Erik,

In follow-up to our teleconference on Thursday, December 16th, 2010, and in anticipation of our call tomorrow I wanted to follow-up on the action points.

1. Attached you will find a letter from (b) (4) explaining the Table under question and the confusion surrounding the data in the various columns. We will be revising this data set and send that to the Agency as an amendment prior to December 31st. As stated in the letter by (b) (4), the "uncoded" AE's are in fact duplicates. The dataset we will be sending you will have all of the adverse events reported to us and you will be able to replicate the tables in the study report. This in no way will change the Tables. Also attached are the instruction on how to log on to the WebX. We thought that might help our discussion tomorrow. We will also be sending by email the data set that will be sent as a formal amendment. I will send that under a separate email.
2. We have obtained all of the Specimen Transfer CRFS for every course and we will be sending this to you along with the amendment.
3. We will revise the EX.xpt dataset and the EXDOSE be the "Amount of EXTRT administered or given". We will resubmit the EX.xpt dataset and all other affected datasets as well as the one affected listing.



EUSA AE Clarification
Letter.docx



(b) (4) Conference
System.docx

We hope that the amendment will lay to rest any confusion.

Regards,

Paul

Paul V. Plourde, MD
Senior Vice President
Global Medical Oncology &
US Medical Affairs Head
EUSA Pharma
One Summit Square Suite 201
1717 Langhorne Newtown Road
Langhorne, PA 19047
Phone: 215 867-4923
Fax: 215 579-0384

(b) (6)

17 December 2010

Paul V. Plourde, MD
Senior Vice President
Global Medical Oncology &
US Medical Affairs Head
EUSA Pharma
One Summit Square Suite 201
1717 Langhorne Newtown Road
Langhorne, PA 19047

Dear Dr. Plourde;

This letter is to serve as a formal follow-up of the issue escalated to me on 17 December 2010 regarding the presence of un-coded adverse event data included in the AE transport file for the current Erwinaze BLA, reference 125,359. I can certainly understand the concern that there are potentially adverse events in the data base that are not being reported because they are not coded; however, we have investigated fully and can assure you this is not the case and all adverse events are indeed reported. There are in fact duplicate records in the data file. This duplication arose from the inclusion of 'source' data and data from the adjudicated pharmacovigilance database in the file. This 'source' data was included as separate records. The analysis is based on the data from the pharmacovigilance data base only, as this captures all the adverse events from the study, is coded, and been fully adjudicated.

I have had an opportunity to review in detail the data and discuss with the team. It is clear that the data set in question includes both un-coded and coded adverse event data and that the un-coded data are duplicate records. The coded data is identified using the AECAT variable. All coded data is identified with a value of 'PHARMACOVIGILANCE' in the AECAT variable. This subset of the file is what was used to the Adverse Event related outputs for this submission and includes all adverse events.

The un-coded data is also included in this file and is identified with a value of 'GENERAL' in the AECAT variable. This data was not used in the production of adverse event related outputs for the submission. To be clear, all of these un-coded events are captured in the coded data and are in fact duplicate records. This reconciliation was done by (b) (4) and EUSA as part of the AE reconciliation process. We were able to confirm this reconciliation earlier today with Taheri Mercedes at EUSA.

The inclusion of the coded and un-coded data in this file was a team decision between EUSA and (b) (4). The intent was to provide clarity into the source of the AE data. Unfortunately, the fact these are included as separate records in the data file has only caused confusion. In retrospect, it would have been best to limit the file to include only the coded data. We will provide an updated version of this file that only includes coded values. To be clear, this file will include all adverse events identified during the course of these studies. The elimination of un-coded data will not exclude any adverse events from reporting. This revision only impacts that data file. Tables and other statistical outputs were based on the coded data and are not impacted.

Attached to this letter is a screen shot from the transport file. From this, it should be easy to see the duplication of records within a subject. For each coded record, there is a corresponding un-coded record as well. For example, the first two records are for subject 787968. One of these is a coded record and the other is the corresponding un-coded record. The un-coded term is '5128.077:Infection...' and the coded term is Grade 3: Blood Infection. These records correspond to the same adverse event. You can see from this screen shot that this pattern of duplication continues across the other records.

I am happy to discuss further and provide additional documentation, if needed. I am travelling the next two weeks. I am accessible via my mobile at (b) (6) and via email at (b) (4)

Sincerely,

(b) (4)

STUDYID	DOMAIN	USUBJID	AESCC	AEREF10	AESTDTC	AESR10	AECAT	AETERM	AEDECD	AEPRESP	AEBODSYS
26	AALL07P2	AE	AALL07P2-019-787968	1	1	2009-12-11	GENERAL	5128.077: INFECTION (CLINICAL OR M	5128.077: INFECTION (CLINICA	Y	
27	AALL07P2	AE	AALL07P2-019-787968	2	EUS-2009-	2009-12-11	PHARMACOV	GRADE 3 BLOOD INFECTION	SEPSIS	N	INFECTION
28	AALL07P2	AE	AALL07P2-019-787968	3	2	2010-01-08	GENERAL	6119.000: FEBRILE NEUTROPENIA (FEV	6119.000: FEBRILE NEUTROPENI	Y	
29	AALL07P2	AE	AALL07P2-019-787968	4	EUS-2010-	2010-01-08	PHARMACOV	GRADE 3 FEBRILE NEUTROPENIA	FEBRILE NEUTROPENIA	N	BLOOD AND
30	AALL07P2	AE	AALL07P2-022-790097	1	1	2009-07-27	GENERAL	4084.000: VOMITING	4084.000: VOMITING	Y	
31	AALL07P2	AE	AALL07P2-022-790097	2	EUS-2010-	2009-07-27	PHARMACOV	GRADE 2 VOMITING	VOMITING	N	GASTROINT
32	AALL07P2	AE	AALL07P2-022-790097	3	2	2009-08-09	GENERAL	6346.001: MOOD ALTERATION - ABITAT	6346.001: MOOD ALTERATION -	Y	
33	AALL07P2	AE	AALL07P2-022-790097	4	EUS-2010-	2009-08-09	PHARMACOV	MOOD ALTERATION-ABITATION	MOOD ALTERED	N	PSYCHIATR
34	AALL07P2	AE	AALL07P2-024-792125	1	2	2009-08-04	GENERAL	5726.000: BILIRUBIN; BILIRUBIN (HY	5726.000: BILIRUBIN; BILIRUB	Y	
35	AALL07P2	AE	AALL07P2-024-792125	2	EUS-2010-	2009-08-04	PHARMACOV	HYPERBILIRUBINEMIA	HYPERBILIRUBINAEMIA	N	HEPATOBI
36	AALL07P2	AE	AALL07P2-024-792125	3	1	2009-08-06	GENERAL	6742.000: HYPERGLYCEMIA; GLUCOSE,	6742.000: HYPERGLYCEMIA; GLU	Y	
37	AALL07P2	AE	AALL07P2-024-792125	4	EUS-2010-	2009-08-06	PHARMACOV	HYPERGLYCEMIA; GLUCOSE, SERUM-HIGH	HYPERGLYCEMIA	N	METABOLIS
38	AALL07P2	AE	AALL07P2-024-792125	6	3	2009-09-16	GENERAL	5726.000: BILIRUBIN; BILIRUBIN (HY	5726.000: BILIRUBIN; BILIRUB	Y	
39	AALL07P2	AE	AALL07P2-024-792125	6	EUS-2010-	2009-09-16	PHARMACOV	HYPERBILIRUBINEMIA	HYPERBILIRUBINAEMIA	N	HEPATOBI
40	AALL07P2	AE	AALL07P2-026-791109	1	1	2009-09-11	GENERAL	1010.000: ALLERGIC REACTION/HYPERS	1010.000: ALLERGIC REACTION/	Y	
41	AALL07P2	AE	AALL07P2-026-791109	2	EUS-2010-	2009-09-11	PHARMACOV	ALLERGIC REACTION/HYPERS	HYPERSENSITIVITY	N	IMMUNE SY
42	AALL07P2	AE	AALL07P2-027-792906	1	1	2009-11-06	GENERAL	1010.000: ALLERGIC REACTION/HYPERS	1010.000: ALLERGIC REACTION/	Y	
43	AALL07P2	AE	AALL07P2-027-792906	2	EUS-2010-	2009-11-06	PHARMACOV	ALLERGIC REACTION/HYPERS	HYPERSENSITIVITY	N	IMMUNE SY
44	AALL07P2	AE	AALL07P2-028-791975	1	1	2010-01-18	GENERAL	6128.077: INFECTION (CLINICAL OR M	6128.077: INFECTION (CLINICA	Y	
45	AALL07P2	AE	AALL07P2-028-791975	2	EUS-2010-	2010-01-18	PHARMACOV	BLOOD INFECTION	SEPSIS	N	INFECTION
46	AALL07P2	AE	AALL07P2-028-791975	3	2	2010-01-18	GENERAL	1646.000: LEUKOCYTES (TOTAL WBC)	1646.000: LEUKOCYTES (TOTAL	Y	
47	AALL07P2	AE	AALL07P2-028-791975	4	4	2010-01-18	GENERAL	1670.000: PLATELETS	1670.000: PLATELETS	Y	
48	AALL07P2	AE	AALL07P2-028-791975	5	EUS-2010-	2010-01-18	PHARMACOV	LEUKOCYTES (TOTAL WBC)	WHITE BLOOD CELL DISORDER	N	BLOOD AND
49	AALL07P2	AE	AALL07P2-028-791975	6	9	2010-01-18	GENERAL	1664.000: NEUTROPHILS/GRANULOCYTES	1664.000: NEUTROPHILS/GRANUL	Y	
50	AALL07P2	AE	AALL07P2-028-791975	7	EUS-2010-	2010-01-18	PHARMACOV	NEUTROPHILS/GRANULOCYTES (ANC/AGC)	NEUTROPHIL COUNT ABNORMAL	N	INVESTIGA
51	AALL07P2	AE	AALL07P2-028-791975	8	EUS-2010-	2010-01-19	PHARMACOV	PLATELETS	PLATELET DISORDER	N	BLOOD AND
52	AALL07P2	AE	AALL07P2-035-793426	1	EUS-2009-	2009-10-22	PHARMACOV	GRADE 3 INFECTION UPPER AIRWAY WIT	UPPER RESPIRATORY TRACT INFE	N	INFECTION
53	AALL07P2	AE	AALL07P2-040-794765	1	1	2010-01-20	GENERAL	1010.000: ALLERGIC REACTION/HYPERS	1010.000: ALLERGIC REACTION/	Y	
54	AALL07P2	AE	AALL07P2-040-794765	2	EUS-2010-	2010-01-20	PHARMACOV	ALLERGIC REACTION/HYPERS	HYPERSENSITIVITY	N	IMMUNE SY
55	AALL07P2	AE	AALL07P2-040-794765	3	2	2010-01-27	GENERAL	9468.000: URTICARIA (HIVES, WELTS,	9468.000: URTICARIA (HIVES,	Y	
56	AALL07P2	AE	AALL07P2-040-794765	4	EUS-2010-	2010-01-27	PHARMACOV	URTICARIA (HIVES,WELTS, WHEALS)	URTICARIA	N	SKIN AND
57	AALL07P2	AE	AALL07P2-041-795656	1	1	2009-12-09	GENERAL	4084.000: VOMITING	4084.000: VOMITING	Y	
58	AALL07P2	AE	AALL07P2-041-795656	2	EUS-2010-	2009-12-09	PHARMACOV	VOMITING	VOMITING	N	GASTROINT



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

Memorandum

Date: 12/16/10 *SL 12/16/10*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: EUSA Pharma (STN 125359/0); tcon regarding clinical dataset issues

FDA ATTENDEES:

Erik Laughner, RPM
Patricia Keegan, Director
Patricia Dinndorf, Clinical Reviewer
Suzanne Demko, Clinical Team Leader
Jeff Summers, Deputy Director of Safety
Anne Pilaro, Supervisory Toxicologist
Dubravka Kufirin, Nonclinical Reviewer

EUSA PHARMA ATTENDEES:

Paul Plourde SVP EUSA
Tim Corn CMO
Taheri Mercedes Pharmacovigilience

(b) (4)

(b) (4)

BACKGROUND:

FDA requested a tcon to discuss 3 pre-filing clinical deficiencies with EUSA Pharma for BLA STN 125359 (Erwinaze). These comments (blue) were provided to EUSA Pharma in advance of the teleconference. The discussion is captured below each FDA written information request comment.

DISCUSSION:

The Safety data is not presented in an acceptable format that will allow substantive review:

- Regarding the AE.xpt and ADAE.xpt datasets for AALL07P2 - These were prepared incorrectly. There are multiple entries in the AEBODSYS column designated "uncoded." The data in the column AETERM should be the verbatim term. The data supplied by COG for the AALL07 P2 trial, or the adverse events reported in sections 8 through 12 of the

case report forms for the EMTP. The terms in the AEDECODE should be coded by EUSA Pharma matching the verbatim term in the AETERM column to preferred terms from the MedDRA coding dictionary. Once the AEDECODE term has been identified the rest of the MedDRA hierarchy is defined. Please include all MedDRA hierarchy in the revised datasets, that is SOC, HLGT, HLT, and PT(AEDECODE). FDA advises you to identify a consultant who is familiar with MedDRA coding to assist.

Discussion: FDA noted that the October advice letter had identified this deficiency, but EUSA Pharma did not provide an adequate response in their November amendment. FDA clarified that all COG safety datasets need to contain the verbatim term and every level of MedDRA hierarchy. For every table/chart etc., that is provided in the BLA which is derived from actual data, FDA must be able to reproduce the results from the datasets. FDA noted that the BLA filing deadline was approaching and it was critical to get a sense on how fast this issue can be addressed by EUSA Pharma. FDA requested that EUSA Pharma provide a name and contact number for the individual(s) who created the datasets. FDA would like to then schedule a tcon early the next week to go thru the datasets with that person to try and resolve this issue. EUSA Pharma committed to providing the contact to FDA by 11AM Friday (December 17, 2010) and noted that they would be ready at any time to discuss next week.

The PK data is not presented in an acceptable format that will allow substantive review:

- Provide Specimen Transfer CRFs for every course of therapy the patients received not just the initial course.

Discussion: EUSA Pharma acknowledged that this information was not provided as previously requested by FDA. EUSA committed to provide FDA a proposed submission target to FDA by 11 AM Friday (December 17, 2010).

- Revise the EX.xpt dataset. The EXDOSE should be the “Amount of EXTRT administered or given.” This is the dose from the Specimen Transfer CRF documented in the “Calculated Dose” space. There should be one line of data for each administration of Erwinaze with the date and the time of administration.

Discussion: EUSA Pharma acknowledged that this information was not provided and agreed to submit to the BLA by early next week.



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

Memorandum

Date: 12/16/10 ^{ESL}
12/16/10
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: EUSA Pharma (USA); BLA STN 125359/0; FDA information request/advice
re: clinical data sets

From: Laughner, Erik
Sent: Thursday, December 16, 2010 10:48 AM
To: Paul Plourde
Cc: Tim Corn
Subject: Items for Discussion Today; STN 125359

Paul,

In advance of today's tcon, FDA would like to discuss these two potential clinical issues with the BLA:

The Safety data is not presented in an acceptable format that will allow substantive review.

- Regarding the AE.xpt and ADAE.xpt datasets for AALL07P2 - These were prepared incorrectly. There are multiple entries in the AEBODSYS column designated "uncoded." The data in the column AETERM should be the verbatim term. The data supplied by COG for the AALL07 P2 trial, or the adverse events reported in sections 8 through 12 of the case report forms for the EMTP. The terms in the AEDECODE should be coded by EUSA Pharma matching the verbatim term in the AETERM column to preferred terms from the MedDRA coding dictionary. Once the AEDECODE term has been identified the rest of the MedDRA hierarchy is defined. Please include all MedDRA hierarchy in the revised datasets, that is SOC, HLG, HLT, and PT(AEDECODE). FDA advises you to identify a consultant who is familiar with MedDRA coding to assist.

The PK data is not presented in an acceptable format that will allow substantive review.

- Provide Specimen Transfer CRFs for every course of therapy the patients received not just the initial course.
- Revise the EX.xpt dataset. The EXDOSE should be the "Amount of EXTRT administered or given." This is the dose from the Specimen Transfer CRF documented in the "Calculated Dose" space. There should be one line of data for each administration of Erwinaze with the date and the time of administration.

If possible, FDA would like to provide a proposed timeframe to fix these items.

Please confirm receipt.

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393

erik.laughner@fda.hhs.gov

<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

If you have received this message in error, do not use, disclose, reproduce, or distribute this message (including any attachments) and notify me immediately. Thank you.



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

Memorandum

DATE of DECISION: December 15, 2010

FROM: Patricia Keegan, M.D.
Director
Division of Biological Oncology Products
Office of Oncology Drug Products
Office of New Drugs
Center for Drug Evaluation and Research

SUBJECT: Designation of BLA application review status

Applicant: EUSA Pharma (USA), Inc.
Product: ERWINAZE

Indication: Treatment of patients with acute lymphoblastic leukemia
(ALL) who have developed hypersensitivity to (b) (4) *E. coli*-
derived asparaginase.

TO: BLA file STN 125359/0

The review status of this file submitted as a BLA application is designated to be:

Priority (6 Months) Standard (10 Months)

Patricia Keegan, M.D.: Patricia Keegan Date: 12-15-2010



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

Memorandum

Date: December 14, 2010 ^{SL} 12/14/10
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: BLA STN 125359 Erwinaze; Filing Meeting

Regulatory Management

Erik Laughner
Patricia Keegan (Director, DBOP)
Karen Jones (CPMS)

Clinical

Suzanne Demko (CDTL)
Patricia Dinndorf

Nonclinical

Dubravka Kufrin
Anne Pilaro (TL)

Clinical Pharmacology

Jun Yang
Hong Zhao (TL)

Facilities

Anastasia Lolas
Patricia Hughes (TL)

Product

Jacek Cieslak
Serge Beaucage
Susan Kirshner (Immunogenicity)

DBOP Safety Team

Jeff Summers (DDS)
Grace Carmouze (SRPM)

Discussion: Filing meeting was held. Participants were present from all disciplines. The filing review checklists were reviewed by each discipline to determine whether application should be filed. Review milestones and upcoming internal meetings were also discussed.



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

Memorandum

Date: 12/14/10 *ELC 12/14/10*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: EUSA Pharma (USA); BLA STN 125359/0; FDA information request/advice
re: nonclinical repro-tox study proposals

From: Laughner, Erik
Sent: Tuesday, December 14, 2010 9:31 AM
To: Paul Plourde
Subject: STN 125359 (Nonclinical)

Paul,

The nonclinical group acknowledges this information and requests that you submit for FDA comments when the proposed timelines/protocols are ready to go.

Erik

From: Paul Plourde [mailto:Paul.Plourde@eusapharma.com]
Sent: Wednesday, November 24, 2010 3:31 PM
To: Laughner, Erik
Subject: RE: STN 125259 information request

Erik,

Here is a list of studies we are considering and currently getting bids from vendors to do the trials. We should pick a vendor in a couple of weeks and then have them write the protocols.

Is this what you were looking for and should we send this via an amendment?

The proposed studies are:

[REDACTED] (b) (4)

Paul



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

Memorandum

Date: 12/10/10

EL
12/10/10

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: EUSA Pharma (USA); BLA STN 125359; FDA information request/advice re:
Proposed Proper Name

From: Laughner, Erik
Sent: Friday, December 10, 2010 8:35 AM
To: Paul Plourde
Subject: FW: STN 125359 (Erwinaze); Proper Name

Hello Paul,

I have obtained some feedback on your proposed proper names:

(b) (4)

With respect to number 1, FDA would not accept this as it is

(b) (4)

(b) (4)

With respect to number 2, FDA requires some additional rationale as to where you

(b) (4)

I have been advised that you also propose an additional proper name with a 3-4 character prefix that is nonsensical. This prefix should follow by hyphen.

Please confirm receipt.

Sincerely,

Erik

From: Paul Plourde [mailto:Paul.Plourde@eusapharma.com]
Sent: Wednesday, November 17, 2010 2:21 PM
To: Laughner, Erik
Subject: RE: STN 125359 (Erwinaze); Proper Name

Confirmed

Paul V. Plourde, MD
Senior Vice President
Global Medical Oncology &
US Medical Affairs Head
EUSA Pharma
One Summit Square Suite 201
1717 Langhorne Newtown Road
Langhorne, PA 19047
Phone: 215 867-4923
Fax: 215 579-0384

(b) (6)

From: Laughner, Erik [mailto:Erik.Laughner@fda.hhs.gov]
Sent: Tuesday, November 16, 2010 11:04 AM
To: Paul Plourde
Subject: STN 125359 (Erwinaze); Proper Name
Importance: High

Paul,

At this time, FDA provides the following additional guidance regarding your selection of a new proper name for the Erwinaze BLA:

We are requiring the use of a prefix with the "asparaginase" stem as the proper name of the biological product that is the subject of this BLA. Please propose three prefixes (in order of preference) for your nonproprietary name with the following conditions:

- The prefix must be 3 to 4 characters in length, nonpromotional, and devoid of meaning

Please confirm receipt.

Sincerely,

Erik Laughner, RPM

From: Paul Plourde [mailto:Paul.Plourde@eusapharma.com]
Sent: Wednesday, November 10, 2010 10:47 AM
To: Laughner, Erik
Cc: Tim Corn; Harriette Nadler
Subject: Questions on Proper Names

Dear Eric,

Thank you for your advice during our telephone call today on the question of a Proper Name for Erwinaze. I would be grateful if you could clarify:

1. Is it necessary for the Proper Name to have an "ase" ending?
2. Are there any other conventions that we should take into account in proposing a name?
3. In the absence of an Recommended International Nonproprietary Name, are there any issues raised by proposing the (b) (4) ?

Thanks
Paul

Paul V. Plourde, MD
Senior Vice President
Global Medical Oncology &
US Medical Affairs Head
EUSA Pharma
One Summit Square Suite 201
1717 Langhorne Newtown Road
Langhorne, PA 19047
Phone: 215 867-4923
Fax: 215 579-0384

(b) (6)



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

Memorandum

Date: 11/23/10 *ESC 11/23/10*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: EUSA Pharma (USA); BLA STN 125359/0; FDA information request/advice;
re: nonclinical data

From: Laughner, Erik
Sent: Tuesday, November 23, 2010 11:29 AM
To: Paul Plourde
Subject: STN 125259 information request

Hello Paul,

I confirm receipt of your BLA amendment for STN 125359 which contained responses to our information requests. This is currently under review.

FDA would like to clarify that as EUSA Pharma will need to provide the results of completed nonclinical reproductive and developmental toxicity studies to the BLA STN 125359 as soon as they are available, we are requesting that you provide within 2 weeks a proposal listing the studies that will be conducted, as well as a timeline for when these studies will be conducted to the IND file (IND #000290). We also recommend that you submit the draft study protocols for FDA review and comment prior to initiating the embryo-fetal development studies with Erwinaze.

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

If you have received this message in error, do not use, disclose, reproduce, or distribute this message (including any attachments) and notify me immediately. Thank you.



Our STN: BL 125359/0

BLA ACKNOWLEDGEMENT

November 19, 2010

EUSA Pharma (USA), Inc.
Attention: Paul Plourde, M.D.
Senior Vice President, Global Medical Oncology
One Summit Square, Suite 201
1717 Langhorne Newtown Road
Langhorne, PA 19047

Dear Dr. Plourde:

Please refer to your rolling Biologics License Application (BLA) submitted under Section 351 of the Public Health Service Act and to your initial September 8, 2010, submission which contained the required non-clinical and clinical portions. We also refer to your November 1, 2010, submission containing the Chemistry, Manufacturing, and Controls (CMC) portion. Your BLA is now considered complete for FDA filing review:

Name of Biological Product: Erwinaze

Our Submission Tracking Number (STN): BL 125359/0

Proposed Use: Treatment of patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to (b) (4) *E. coli*-derived asparaginase.

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the format and content requirements of revised 21 CFR 201.56-57.

We will notify you within 60 days of the receipt date if the application is sufficiently complete to permit a substantive review.

The BLA Submission Tracking Number provided above should be cited at the top of the first page of all submissions to this application.

If you have any questions, please contact the Senior Regulatory Health Project Manager, Erik Laughner, at (301) 796-1393.

Sincerely,

/Karen D. Jones/
Karen D. Jones, on behalf of Patricia Keegan
Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research



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

Memorandum

Date: November 17, 2010 22 11/17/10
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: BLA STN 125359 Erwinaze; Planning Meeting (First Committee Meeting)

Regulatory Management

Erik Laughner
Patricia Keegan (Director, DBOP)

Clinical

Suzanne Demko (CDTL)
Patricia Dinndorf

Nonclinical

Dubravka Kufirin
Anne Pilaro (TL)

Clinical Pharmacology

Jun Yang
Hong Zhao (TL)

Facilities

Mary Farbman
Anastasia Lolos
Patricia Hughes (TL)

Product

Jacek Cieslak
Serge Beaucage
Susan Kirshner (immunogenicity TL)

OSE

Sue Kang
Todd Bridges (DMEPA)
Loretta Holmes (DMEPA)

Discussion: Planning meeting was held. Participants were present from all disciplines. The content/structure of eCTD BLA, timelines for review of applicant, needed consults, 21st Century GRMP review dates were discussed. Early issues/deficiencies identified were discussed by team.



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

Memorandum

Date: 11/16/10 *ESL 11/16/10*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: EUSA Pharma (USA); BLA STN 125359/0; FDA advice/information request
re: Proposed Proper Name

From: Laughner, Erik
Sent: Tuesday, November 16, 2010 11:04 AM
To: Paul Plourde
Subject: STN 125359 (Erwinaze); Proper Name
Importance: High

Paul,

At this time, FDA provides the following additional guidance regarding your selection of a new proper name for the Erwinaze BLA:

We are requiring the use of a prefix with the "asparaginase" stem as the proper name of the biological product that is the subject of this BLA. Please propose three prefixes (in order of preference) for your nonproprietary name with the following conditions:

- The prefix must be 3 to 4 characters in length, nonpromotional, and devoid of meaning

Please confirm receipt.

Sincerely,

Erik Laughner, RPM

From: Paul Plourde [mailto:Paul.Plourde@eusapharma.com]
Sent: Wednesday, November 10, 2010 10:47 AM
To: Laughner, Erik
Cc: Tim Corn; Harriette Nadler
Subject: Questions on Proper Names

Dear Eric,

Thank you for your advice during our telephone call today on the question of a Proper Name for Erwinaze. I would be grateful if you could clarify:

1. Is it necessary for the Proper Name to have an "ase" ending?
2. Are there any other conventions that we should take into account in proposing a name?

3. In the absence of an Recommended International Nonproprietary Name, are there any issues raised by proposing the [REDACTED] (b) (4)

Thanks

Paul

Paul V. Plourde, MD
Senior Vice President
Global Medical Oncology &
US Medical Affairs Head
EUSA Pharma
One Summit Square Suite 201
1717 Langhorne Newtown Road
Langhorne, PA 19047
Phone: 215 867-4923
Fax: 215 579-0384

[REDACTED] (b) (6)



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

Memorandum

Date: 11/12/10 *ELL 11/12/10*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: EUSA Pharma (USA); BLA STN 125359/0; FDA information request re:
proposed labeling indications

From: Laughner, Erik
Sent: Friday, November 12, 2010 8:44 AM
To: Paul Plourde
Subject: BLA STN 125359; User Fee Issue
Importance: High

Dear Paul,

The proposed label for Erwinaze has listed 2 indications for use. The only indication which has Orphan status is ALL.

The second proposed indication of [REDACTED] (b) (4).

We assume that as FDA only discussed an indication for ALL, you will wish to withdraw this second non-ALL indication as it will require data to justify.

If this is the case, please provide by Wednesday of next week an amendment to the BLA stating your intention to withdraw this second indication and revised labeling (including SPL and word) which reflects this.

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

If you have received this message in error, do not use, disclose, reproduce, or distribute this message (including any attachments) and notify me immediately. Thank you.



IND 000290
BLA 125359

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

EUSA Pharma (USA), Inc.
One Summit Square, Suite 201
1717 Langhorne-Newtown Road
Langhorne, Pennsylvania 19407

ATTENTION: Paul Plourde, MD
Senior Vice President, Global Medical Oncology

Dear Dr. Plourde:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act and to your Biologics License Application (BLA) dated October 29, 2010, received November 1, 2010 submitted under section 351 of the Public Health Service Act for Erwinia L-asparaginase Injection, 10,000 International Units per vial.

We also refer to your May 13, 2010, IND correspondence, received May 14, 2010, and to your November 8, 2010, BLA correspondence, received November 9, 2010, requesting review of your proposed proprietary name, Erwinaze.

We have completed our review of the proposed proprietary name, Erwinaze and have concluded that it is acceptable.

The proposed proprietary name, Erwinaze, will be re-reviewed 90 days prior to the approval of the BLA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your November 8, 2010 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted to your BLA for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Erik Laughner at (301) 796-1393.

Sincerely,

{See appended electronic signature page}

Denise P. Toyer, PharmD

Deputy Director

Division of Medication Error Prevention and Analysis

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DENISE P TOYER
11/10/2010



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

Memorandum

Date: 11/03/10 *sc 11/03/11*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: EUSA Pharma (USA); BLA STN 125359/0; FDA Advice regarding PDUFA clock start

From: Laughner, Erik
Sent: Wednesday, November 03, 2010 4:22 PM
To: Paul Plourde
Subject: RE: CMC BLA

Hello Paul,

I have rec'd the load for the CMC portion of the rolling BLA. While you didn't explicitly state in your cover letter that EUSA Pharma considers the BLA to be complete, per prior communications, we will do so and trigger the formal PDUFA clock. A review schedule will be determined shortly and you will be notified.

Sincerely,

Erik Laughner, RPM

From: Paul Plourde [mailto:Paul.Plourde@eusapharma.com]
Sent: Sunday, October 31, 2010 11:31 AM
To: Laughner, Erik
Subject: CMC BLA

Erik,

Just to give you a heads up that the CMC portion of the Erwinaze BLA will be coming to the Agency either on Tuesday or Wednesday of this coming week.

Paul

Paul V. Plourde, MD
Senior Vice President
Global Medical Oncology &
US Medical Affairs Head
EUSA Pharma
One Summit Square Suite 201
1717 Langhorne Newtown Road
Langhorne, PA 19047
Phone: 215 867-4923
Fax: 215 579-0384



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125359/0

INFORMATION REQUEST

October 28, 2010

EUSA Pharma (USA), Inc.
Attention: Paul Plourde, M.D.
Senior Vice President, Global Medical Oncology
One Summit Square, Suite 201
1717 Langhorne Newtown Road
Langhorne, PA 19047

Dear Dr. Plourde:

This letter is in regard to your rolling biologics license application for ERWINAZE (Erwinia L-asparaginase) submitted under Section 351 of the Public Health Service Act. To date, you have submitted the non-clinical and clinical portions of this application. Although the formal review clock will not start until the date on which you submit the final Chemistry, Manufacturing, and Controls (CMC) portion and inform us that your application is complete, we now provide the following preliminary comments and information requests. Please note that these issues should be rectified as soon as possible.

Financial Disclosure:

1. As the applicant, you did not provide required FDA form 3454 and/or 3455. Please refer to Guidance for Industry: Financial Disclosure by Clinical Investigations (<http://www.fda.gov/RegulatoryInformation/Guidances/ucm126832.htm>).
2. Forty-five financial disclosure forms [1.3.4] were included in your submission representing investigators from 7 of the 31 institutions participating in the study. Only 3 were from the individual identified as the Institutional PI. The form for (b) (6) did not have A or B checked off. Submit the financial disclosure forms from all institutions who contributed patients to the study.

Clinical Data:

3. In the AALL07P2 study, we could not identify the institution where a patient was treated. Either identify the specific location within the BLA where there is a table in the Study Report that lists the treatment sites for individual subjects or provide such a table.

4. At the September 3, 2009 pre-BLA meeting, we requested that complete case report forms (CRFs) from all patients enrolled in ALL07P2 study be submitted and you agreed that this information would be provided in the BLA submission. However, there are CRFs for only 16 patients on the AALL07P2 study in the BLA. In addition, the CRFs submitted do not contain any information regarding the actual dose and the actual date Erwinaze was administered. Submit CRFs for all patients from the ALL07P2 study and provide actual Erwinaze dose and date of administration for each patient treated.
5. Although the "Reviewer's Guide" states the CRFs for the EMTP study are provided in the traditional bookmarked/hyperlinked format, this is not the case. Provide hyperlinks to the corresponding CRF whenever a subject is mentioned in the study report.
6. Although the "Reviewer's Guide" states each patient's CRF file is named with the patient's unique identification number, the identification code of the patients in the EMTP study listed in the electronic index of the application does not match the identification code of patients in the narratives included in the EMTP study synopsis or the identification code in the datasets. An individual subject should be identified in the electronic index of the application, in the EMTP study synopsis (narratives) and in the EMTP study datasets with an identical code. Revise the submission to permit easy navigation through these elements.
7. The application does not contain any information about concomitant medications. Please provide this information for all patients.
8. The documents named "icon1.gif, icon2.gif, icon3.gif do not open. For example, see section 5.3.4.3.25.1.1 for AALL07P2. Please correct this.

Clinical Datasets:

9. Regarding the DM.xpt dataset for AALL07P2, the variable SITEID should be a unique identifier for each treatment site, not a unique number for each subject. There were 31 institutions participating, so there should not have been more than 31 unique identifiers. Revise the DM.xpt dataset to include a unique identifier for each of the 31 institutions participating. Include a table in the study report that lists the participating institutions, with the unique site identifying code and the subject identification codes for patients treated at the individual institutions.
10. For the Define.xls dataset for AALL07P2, the document in the application consists of lines of codes (e.g. `?xml version="1.0"encoding="ISO-8859-1" ?> + <xsl:stylesheet version="1.0" xmlns:odm=http://www.cdisc.org/ns/odm/v1.2xmlns:xsl="http://www.w3.org/1999/XSL/Transform . . .?').`

The define document should be a pdf document not an xls document. The document should provide definitions for the datasets and contain hyperlinks to the datasets. Revise the define document.

11. Regarding the AE.xpt and ADAE.xpt datasets for AALL07P2:

- a. Please explain why are there 10 more lines of AEs in ADAE.xpt (98) than in AE.xpt (88).
- b. There are 20 items in the AEBODSYS column identified as “Uncoded.” See table below:

AETERM	AEDECOD	AEBODSYS	N Row
1010.000: ALLERGIC REACTION/HYPERSENSITIVITY (INCLUDING DRUG FEVER)	1010.000: ALLERGIC REACTION/HYPERSENSITIVITY (INCLUDING DRUG FEVER)	Uncoded	4
1646.000: LEUKOCYTES (TOTAL WBC)	1646.000: LEUKOCYTES (TOTAL WBC)	Uncoded	1
1664.000: NEUTROPHILS/GRANULOCYTES (ANC/AGC)	1664.000: NEUTROPHILS/GRANULOCYTES (ANC/AGC)	Uncoded	1
1670.000: PLATELETS	1670.000: PLATELETS	Uncoded	1
2810.000: FATIGUE (ASTHENIA, LETHARGY, MALAISE)	2810.000: FATIGUE (ASTHENIA, LETHARGY, MALAISE)	Uncoded	3
2817.000: FEVER (IN THE ABSENCE OF NEUTROPENIA, WHERE NEUTROPENIA IS DEFINED AS ANC <1.0 X 10E9/L)	2817.000: FEVER (IN THE ABSENCE OF NEUTROPENIA, WHERE NEUTROPENIA IS DEFINED AS ANC <1.0 X 10E9/L)	Uncoded	1
3444.001: DERMATITIS: RASH: DERMATITIS ASSOCIATED WITH RADIATION - CHEMORADIATION	3444.001: DERMATITIS: RASH: DERMATITIS ASSOCIATED WITH RADIATION - CHEMORADIATION	Uncoded	1
3458.000: URTICARIA (HIVES, WELTS, WHEALS)	3458.000: URTICARIA (HIVES, WELTS, WHEALS)	Uncoded	1
4062.000: NAUSEA	4062.000: NAUSEA	Uncoded	2
4084.000: VOMITING	4084.000: VOMITING	Uncoded	5
5119.000: FEBRILE NEUTROPENIA (FEVER, UNK. ORIGIN,W/O INFECTION,ANC<1X10E9, FEVER>=38.5°C)	5119.000: FEBRILE NEUTROPENIA (FEVER, UNK. ORIGIN,W/O INFECTION,ANC<1X10E9, FEVER>=38.5°C)	Uncoded	1
5128.077: INFECTION (CLINICAL OR MICROBIOLOGICAL DX) W/ GR 3-4 NEUTROPHILS, ANC<1.0X10E9 - BLOOD	5128.077: INFECTION (CLINICAL OR MICROBIOLOGICAL DX) W/ GR 3-4 NEUTROPHILS, ANC<1.0X10E9 - BLOOD	Uncoded	2
5137.077: INFECTION WITH NORMAL ANC OR GRADE 1 OR 2 NEUTROPHILS - BLOOD	5137.077: INFECTION WITH NORMAL ANC OR GRADE 1 OR 2 NEUTROPHILS - BLOOD	Uncoded	1
5712.000: ALBUMIN, SERUM-LOW (HYPOALBUMINEMIA)	5712.000: ALBUMIN, SERUM-LOW (HYPOALBUMINEMIA)	Uncoded	3
5718.000: ALT, SGPT (SERUM GLUTAMIC PYRUVIC TRANSAMINASE)	5718.000: ALT, SGPT (SERUM GLUTAMIC PYRUVIC TRANSAMINASE)	Uncoded	4
5722.000: AST: AST, SGOT(SERUM GLUTAMIC OXALOACETIC TRANSAMINASE)	5722.000: AST: AST, SGOT(SERUM GLUTAMIC OXALOACETIC TRANSAMINASE)	Uncoded	3
5726.000: BILIRUBIN: BILIRUBIN (HYPERBILIRUBINEMIA)	5726.000: BILIRUBIN: BILIRUBIN (HYPERBILIRUBINEMIA)	Uncoded	3
5742.000: HYPERGLYCEMIA: GLUCOSE, SERUM-HIGH (HYPERGLYCEMIA)	5742.000: HYPERGLYCEMIA: GLUCOSE, SERUM-HIGH (HYPERGLYCEMIA)	Uncoded	3
6346.001: MOOD ALTERATION - AGITATION	6346.001: MOOD ALTERATION - AGITATION	Uncoded	1

AEDECOD should be a MEDRA preferred term (PT), these are not. Code numbers should not be included. For individual subjects, we should be able to check the CRF and confirm that the AETERM matches that reported in the CRF. The submission only contains CRFs for 16 patients enrolled on the AALL07P2 study. Please revise the submissions to correct these columns of the datasets, and submit CRFs for all subjects enrolled on the AALL07P2 study.

12. Regarding the EX.xpt and ADEX.xpt datasets for AALL07P2:

- a. The value in EXDOSE should be the individual dose the subject actually received, not the theoretical dose.
- b. There should be one line of data for each dose with the date the dose was administered.

- c. In ADEX.xpt, the Column DOSE appears to be a calculated theoretical individual dose the subject received. These doses do not correspond to the doses calculated (Calculated Dose from BSA) for individual subjects using the initial height and weight to determine the BSA. See table below:

USUBJID	DOSE from ADEX	Calculated Dose from BSA	Difference
AALL07P2-001-785035	25000	18074	6926
AALL07P2-002-785414	25157	39922	-14765
AALL07P2-003-786636	25397	15849	9548
AALL07P2-004-785017	25000	16126	8874
AALL07P2-005-787137	24545	26525	-1980
AALL07P2-006-787073	25000	30528	-5528
AALL07P2-007-787538	25000	31613	-6613
AALL07P2-008-788007	25000	28262	-3262
AALL07P2-009-790770	24834.44	37655	-12821
AALL07P2-010-788317	24153	58953	-34800
AALL07P2-011-788890	24887	55004	-30117
AALL07P2-012-787136	25223	28018	-2795
AALL07P2-013-787221	25000	44127	-19127
AALL07P2-014-790047	25260	24150	1110
AALL07P2-015-787929	25000	47943	-22943
AALL07P2-016-789794	25417	61380	-35963
AALL07P2-017-791449	25000	33418	-8418
AALL07P2-018-789742	25000	36032	-11032
AALL07P2-019-787968	25000	17979	7021
AALL07P2-021-788249	25000	36808	-11808
AALL07P2-022-790037	25000	17680	7320
AALL07P2-023-791030	25000	22348	2652
AALL07P2-024-792125	25000	25528	-528
AALL07P2-025-791771	25000	16312	8688
AALL07P2-026-791109	25000	35968	-10968
AALL07P2-027-792906	25000	21894	3106
AALL07P2-028-791975	25000	26508	-1508
AALL07P2-030-790945	24299	26854	-2555
AALL07P2-031-791637	25255	48886	-23631
AALL07P2-032-789461	25000	15186	9814
AALL07P2-033-791194	25000	16474	8526
AALL07P2-034-792798	25000	17619	7381
AALL07P2-035-793425	25758	16466	9292
AALL07P2-036-790620	26000	31225	-5225
AALL07P2-037-793008	23125	18507	4618
AALL07P2-038-794013	25000	25877	-877
AALL07P2-039-794101	25000	17520	7480
AALL07P2-040-794765	23256	53854	-30598
AALL07P2-041-795635	24155	51767	-27612
AALL07P2-042-794669	25000	16211	8789
AALL07P2-045-793370	25000	33175	-8175
AALL07P2-047-795256	15625	36811	-21186
AALL07P2-048-794165	23438	16134	7304
AALL07P2-049-795239	25000	41900	-16900
AALL07P2-050-795638	25000	22535	2465
AALL07P2-051-797078	25000	13575	11425
AALL07P2-052-794813	24390	51239	-26849
AALL07P2-053-794966	25078	15949	9129
AALL07P2-054-798844	25000	46906	-21906
AALL07P2-055-796945	25000	46638	-21638
AALL07P2-056-798278	24681	58740	-34059
AALL07P2-057-793635	25000	31448	-6448
AALL07P2-058-796268	25000	27194	-2194

For example, as documented in the AE CRF for Subject 785017, "On 16 Mar 2009, the patient started Erwinaze 16,000 IU intramuscular injection three times weekly for 6 doses." This dose corresponds to the dose we calculated (see table above), 16126 IU, but not the reported dose of 25000 IU. Please explain these discrepancies and revise the datasets. Submit CRFs from all patients documenting details of Erwinaze administration.

13. Regarding Data Tabulation Data Definition (5.3.4.2.25.1.2) for AALL07P2:
- a. The Table of Contents includes “Annotated Case Report Form.” We are unable to navigate to this section using the link from the side bar Table of Contents.
 - b. The “Dataset Metadata” Location links should allow navigation to the datasets. These are presented as CO.XPT rather than CO.xpt.
 - c. The links to “CRF” in the Origin column of the “Variable Metadata” and “Value Level Metadata” are not functional.

Please correct these problems.

14. The definitions in the Analysis Dataset Definition (5.3.4.2.25.3.3) section for AALL07P2 do not contain enough information. DOSE is identified as “Dose Amount,” “text,” and “FINAL.DA.” There is not enough information to determine what the dose represents or how it was derived. Please revise this document to explicitly define how elements were constructed. Clarify what “FINAL.DA” signifies.

Nonclinical:

15. As a result of the 2010 Patient Protection and Affordable Care Act, the guidance provided to you regarding reliance on previously conducted toxicity studies in published literature, and a potential waiver for conducting further developmental and reproductive toxicity testing of ERWINAZE is no longer an acceptable approach. Your BLA submitted under section 351(a) of the PHS Act includes published literature as an assessment of the potential developmental and reproductive toxicity. Under the new legislation, you may not rely on published literature describing studies of other biological products to fulfill the current regulatory requirements for nonclinical developmental and reproductive toxicity studies with ERWINAZE.

Therefore, we will require that you provide the results from the complete battery of fertility, embryo-fetal and pre/post-natal nonclinical developmental toxicity studies conducted with ERWINAZE in pharmacologically responsive species (refer to ICH S5(R2): Detection of Toxicity to Reproduction for Medicinal Products (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm074950.pdf>) and ICH S6 (R1): Preclinical Evaluation of Biotechnology-Derived Pharmaceuticals (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM194490.pdf>)). We recommend that you submit draft protocols for these studies as an amendment to the BLA for review and comment by the nonclinical reviewers prior to initiation of these studies.

Proper Name:

16. Your proposed proper name [REDACTED] (b) (4)

[REDACTED] (b) (4)

As a result, the following may result:

- a. Medication errors (e.g., the patient receiving a product different than what was intended to be prescribed).
- b. Confusion among healthcare practitioners who may consider use of the same nonproprietary name to mean that the biological products are indistinguishable.
- c. Limitations in the ability to conduct appropriate pharmacovigilance.

To mitigate the above concerns, please propose an alternate proper (nonproprietary) name for consideration.

Establishment Information:

17. Provide a revised FDA Form 356h which contains the required establishment information.

If you have any questions, please contact the Senior Regulatory Health Project Manager, Erik Laughner, at (301) 796-1393.

Sincerely,

/Patricia Keegan/
Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research



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

Memorandum

Date: 09/28/10 *En 01/28/10*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: EUSA Pharma (USA); BLA STN 125359/0; FDA information request re:
Proper Name

From: Laughner, Erik
Sent: Tuesday, September 28, 2010 3:58 PM
To: 'Paul Plourde'
Subject: Erwinaze BLA

Hello Paul,

For the proposed BLA for Erwinaze, can you tell me whether the Proper Name "Erwinia L-asparaginase" is either an approved WHO INN or USAN name?

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/cder/Offices/OODP/about.htm>

If you have received this message in error, do not use, disclose, reproduce, or distribute this message (including any attachments) and notify me immediately. Thank you.



FDA DRAFT RESPONSES

MEETING DATE: December 10, 2009
TIME: 2:00 – 3:00 p.m. ET
APPLICATION: IND 290
SPONSOR: EUSA Pharma (US) Inc. [EUSA Pharma]
DRUG NAME: L-asparaginase (*Erwinia chrysanthemi*) [Erwinase®]
TYPE OF MEETING: Type B, Pre-BLA; Teleconference
MEETING CHAIR: Serge Beaucage
MEETING RECORDER: Erik Laughner

TENTATIVE LIST OF FDA ATTENDEES:

Patricia Keegan	Director, DBOP/OODP
Jeff Summers	Clinical Team Leader, DBOP/OODP
Patricia Dinndorf	Clinical Reviewer, DBOP/OODP
Erik Laughner	Regulatory Project Manager, DBOP/OODP
Serge Beaucage	Supervisory Product Reviewer, DTP/OBP
Jacek Cieslak	Product Reviewer, DTP/OBP
Barry Cherney	Deputy Director, DTP/OBP
Anastasia Lolos	Facilities Reviewer, DMPQ/OC
Patricia Hughes	Lead Facilities, DMPQ/OC
Jun Yang	Clinical Pharmacology Reviewer, DCP5/OCP/OTS
Hong Zhao	Clinical Pharmacology Team Leader, DCP5/OCP/OTS

1.0 MEETING OBJECTIVES:

To obtain concurrence on any outstanding CMC issues and the final elements of the CMC portion of the proposed BLA.

2.0 BACKGROUND

On May 29, 2009, EUSA Pharma requested a Type C, CMC meeting to discuss and reach agreement with FDA on a proposed approach to process validation for drug substance and drug product. Specifically, FDA's assessment of:

1. The use of a Failure Modes & Effects Analysis (FMEA) based approach to identify the critical steps which could impact on key quality attributes such as safety, potency (efficacy) and purity.

2. The intended approach to demonstrate (b) (4) Validation.
3. The approach to demonstrate the Extraction Validation.
4. The approach for Validation of the Purification to demonstrate consistency.
5. Concurrence that the commercial batches to be used for demonstrating consistency and developing both batch and in-process specifications can be released based on the current approved specifications and that final release specifications for the new analytical methods can be set on the basis of the data gathered from the profiling and validation batches.

FDA meeting minutes were issued on September 2, 2009.

On September 30, 2009, EUSA Pharma requested a Pre-BLA CMC meeting to

1. Seek guidance on several remaining CMC items.
2. Discuss the timing of pre-approval inspection in light of the planned shut down for essential maintenance.
3. Seek guidance on the final elements of CMC portion of the proposed BLA.

Disclaimer: This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for December 10, 2009, between EUSA Pharma and the Division of Biologic Oncology Products. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact the Regulatory Project Manager). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Please note that if there are any major changes to your development plan, the purpose of the meeting, or questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting. Draft FDA responses were communicated to EUSA Pharma on December 7, 2009.

3.0 DISCUSSION

SPONSOR SUBMITTED QUESTIONS & PREAMBLE (ITALITCS) AND FDA RESPONSE:

Based on discussions held during the 30 May 2006 preBLA meeting, (b) (4) (b) (4), manufacturer of Erwinase®, has developed and implemented a number of new more sensitive analytical methods. Application of some of the new methodologies to the drug product (DP) and drug substance (DS) has revealed product heterogeneity that is not observed with the less sensitive methods currently used for product release. Heterogeneity was present in all lots of Erwinase® examined, both freshly manufactured batches and older, stored batches. Product heterogeneity was observed primarily on application of Size Exclusion Chromatography (SEC) and Weak Cation Exchange Chromatography (WCX) methods but was also apparent on Reverse Phase Ultra Pure Liquid Chromatography (RP-UPLC).

In order to understand the nature of the product heterogeneity, further characterization was undertaken by collecting fractions from SEC and WCX runs and then analyzing them by Mass Spectrometry (MS), SDS-PAGE and Western Blot. The results demonstrated that much of the product heterogeneity is due to product related substances (classified as such in accordance with ICH Q6B). Most of the individual peaks separated on WCX chromatography were also shown to have asparaginase activity and a Km for the enzyme comparable to Erwinase® reference standard, supporting their classification as product related substances.

The Sponsor therefore proposes that when specifications are developed for drug substance and drug product analysis with these methods, collective criteria be set for those substances that have been identified as product related. Upper and lower limits will be set for each specification. As discussed with the FDA previously, the specifications will be reviewed as more information is gained as additional lots are manufactured and tested with the new methods subsequent to approval. Data on the preliminary characterization of the newly detected product related peaks is presented in Section 10.1.

1. Does the Agency concur with the proposed classification of these peaks as product related substances as per ICH Q6B?

FDA Response: Yes, FDA agrees with EUSA Pharma's assessment that peaks C, D, and E are product related substances.

2. (b) (4)

FDA Response: No, FDA does not agree. Minimally, FDA recommends that each product related substance be monitored to ensure manufacturing consistency although this monitoring may be implemented with action limits rather than specifications. However, aside from impacting on product potency, variants of the desired product may

also affect pharmacokinetics, biodistribution, or the immunogenicity of the product. Because the risk associated with these variants is expected to be different, each attribute should be specified separately unless information is provided to indicate the risk to product performance is the same for the pooled attributes. Please note if the method used introduces artifacts that may compromise the ability of the assay to discern relevant changes in product quality, FDA recommends that EUSA Pharma modify or replace that method.

The manufacturing process for Erwinase® has not been changed and has exhibited consistent product stability for over twenty years. DP batch analysis data demonstrates that the performance of the manufacturing process has been consistent based on testing of the drug product.

In order to assess the consistency as well as to demonstrate that the lots used in the PK/PD study were representative of the manufacturing process, a number of lots (CAMR 134, 135, 144, 145 and 146) were analyzed using the new analytical methods.

The PK/PD study lots (including CAMR134) are older than the profiling/pre-validation lots (CAMR144, 145 and 146) and do demonstrate some differences in the intensity of the peaks in regards to the product related substances which appear to be related to the age of the lots.

A comparison across the two PK/PD lots and the three profiling/pre-validation lots of the data generated using the new methods demonstrate that all five lots are qualitatively and quantitatively, (except for those quantitative differences associated with the historical lots), consistent with one another, as shown in Section 10.2. The data in Section 10.2 demonstrate that the PK/PD lots are representative of the manufacturing process.

3. Does the Agency agree that the data support the conclusion that the PK/PD lots are representative of the manufacturing process?

FDA Response: Due to the limited data provided, FDA cannot make a final determination regarding EUSA's analysis and conclusions. While the information currently available is supportive of EUSA's conclusion, the data presented at this time are not comprehensive enough to determine whether the PK/PD lots are truly representative of the manufacturing process. This issue will be addressed during a complete review of the BLA when all the release, stability and characterization data for these lots are available and can be compared to the historical results and validation lots.

As discussed at the previous meeting with FDA (11 Aug 2009), there has been no change to the manufacturing process for Erwinase® and the product has been used in the clinic for over twenty years. The current drug product has a shelf life of 36 months as approved in the UK Product License No. 4073/0003 and Manufacturer License No. ML/4073/01 and included as part of the IND # 290.

At the request of the Agency to develop more sensitive and discriminatory technologies for the analysis of Erwinase, we have developed and implemented new analytical methods. There are currently six (6) drug product lots on stability. Of these, three lots were put on stability before the 'new' analytical methods were developed. These lots have been analyzed by the current analytical methods at all time points since manufacture and have been or will be analyzed using both the current and the 'new' analytical methods as stability time points are reached. An additional three (3) drug product lots (profiling/pre-validation lots) have been placed on stability since the 'new' analytical methods were developed and implemented. These drug product lots are being tested by both the current and the 'new' methods. In addition, the validation lots will also be put on stability as they are made and tested using current and 'new' methods.

Consequently, at the time of filing of the BLA, data from two (2) lots at 36 months and one (1) lot at 24 months utilizing both the current and the new methods will be submitted along with data from the profiling/pre-validation lots (from time 0 up to 12 months) and validation lots (from time 0 up to 3 months). This information will be updated during the review to include additional data from three lots at 12 months and three lots at 6 months. Appropriate accelerated and photostability data will also be included in the BLA.

There has been significant clinical use of lots that are between 9 months and 28 months old. The lots used in the pivotal PK/PD trial were greater than 15 months old at time of use and exhibit the expected activity associated with efficacy in the PK/PD clinical trial. Other lots dating from 9 months to 28 months post manufacture have been used in the Erwinase Master Treatment Protocol (EMPT) and show the expected safety profile associated with Erwinase® usage. This supports the proposal that the changes observed on stability are only associated with differences in product related substances with no significant impact on safety or efficacy.

4. EUSA proposes to assign a product shelf life based on the stability data from newer lots (0 to 12 months) together with the data from the lots where the new methods were applied after the stability study had commenced (24 and 36 month time points). Does the agency agree with the proposed approach for assigning the shelf life of the product?

FDA Response: Yes, FDA agrees. The proposed approach is acceptable if the manufacturing process has not changed and appropriate product quality is demonstrated for the proposed dating period.

(b) (4) routinely manufactures approximately (b) (4) of Erwinase® drug substance and approximately (b) (4) of Erwinase® drug product per year. This extent of manufacture has proved appropriate to maintain a continuity of supply both to patients in territories where the drug is currently licensed and to other patients with unmet need, including those treated under IND # 290.

To continue to ensure continuity of supply as well as provide the process validation data (as discussed in the August 11, 2009 Type C Meeting) for the BLA, the (b) (4) Manufacturing Program has been modified so that the manufacture of three drug substance and three drug product validation batches is scheduled for (b) (4), with BLA filing projected for June 2010. This manufacturing campaign will then be followed by a facility shutdown during Q2 and Q3 2010 to permit essential maintenance and facility upgrades to be performed. The essential maintenance and facility upgrades include:



- Routine facility maintenance activities

A detailed description of the maintenance and facility upgrades is provided in Section 10.4 together with a summary of the planned validation and/or revalidation activities and a full schedule for the work.

5. Based on the information provided, and given that EUSA will be requesting Priority Review, does the Agency concur that the planned facility upgrades will not impact on the overall BLA review, the Pre-Approval Inspection process and approval timelines?

FDA Response: No, FDA does not concur. The BLA cannot be approved until the review and pre-approval inspection have been conducted and all issues have been resolved. For a 6-month priority review, the inspection should be conducted during the third month of the review cycle or the fourth month at the latest to allow for time to resolve any inspection observations. In addition, the pre-approval inspection must be conducted while the establishment is in operation. Failure to be ready for inspection at the time of the BLA submission could result in a refusal-to-file (RTF) decision by the FDA. FDA recommends that EUSA Pharma delay the submission of the BLA a month or two (July-August) in order to allow for the inspection of the facility in the October-November 2010 time frame.

At the time of filing the BLA the sponsor plans to submit a full package of information describing the manufacturing process (as discussed with FDA in May 2006 and June 2007) along with the results of process validation on three batches of drug substance and three batches of drug product, using the newly developed and validated set of analytical methods studies (as discussed in August 2009 with FDA). A full package of data characterizing the drug substance and drug product will also be included (as discussed with FDA in October 2008).

The BLA will also include stability data based on analysis using the new methods and this will be available for two profiling/pre-validation DP batches held for 12 months, one profiling/pre-validation DP batch held for 9 months and three validation DP batches held for 3 months. The sponsor plans to submit further stability data at the 120 day update point as described in Section 10.5. This plan was previously discussed with FDA in October 2008.

Stability data will also be included for batches CAMR 134 and 135, which will have been analyzed at 36 months and batch CAMR 138 which will have been analyzed at 24 months using the new analytical methods although no time zero data is available for these batches using new methods.

6. Does the Agency have any comments regarding the contents of the 120-day update?

FDA Response: FDA's acceptability of EUSA Pharma's proposal as outlined depends on the timelines for review of the BLA application. If the submission is a priority review then the stability data must be provided in the initial submission. Please note that the 120-day update is intended for submission of new clinical safety information rather than manufacturing data.

ADDITIONAL COMMENTS:

7. FDA notes that lot CAMR127 failed sterility at the 36 time point. EUSA Pharma will need to adequately summarize the outcome of the out-of-specification (OOS) sterility failure on a stability sample at the time of inspection.
8. All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Please include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. An updated manufacturing schedule for both the drug substance and drug product should be provided in the BLA submission to facilitate the planning of the pre-license inspections during the review cycle.

The CMC Drug Substance section of the BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control. The provided information should include, but not be limited to the following:

- Monitoring of bioburden and endotoxin levels at critical manufacturing steps using validated bioburden and endotoxin tests. The pre-determined bioburden and endotoxin limits should be provided (3.2.S.2.4).
- Three successful consecutive product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).
- Column (b) (4) sanitization and storage validation (3.2.S.2.5).
- Bioburden and endotoxin data obtained during manufacture of the three conformance lots (3.2.S.2.5).
- Data summaries of shipping validation studies (3.2.S.2.5).
- Drug substance bioburden and endotoxin release specifications. The bioburden limit should be < 1 CFU/10 mL for bulk materials allowed to be stored for extended periods of time at refrigerated temperatures (3.2.S.4).

The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries to support the (b) (4) processing operations. For guidance on the type of data and information that should be submitted, refer to the 1994 “FDA Guidance for Industry, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products”. Test methods and validation data summaries for the container closure integrity test and preservative effectiveness test (if applicable) should be submitted in Section 3.2.P.2.5 of the submission.

Provide the study protocols and validation data summaries in Section 3.2.P.3.5 for the following:

- (b) (4)
 - (b) (4) equipment and components, and equipment (b) (4) program
 - In-process controls and hold times
 - Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs
 - A description of the routine environmental monitoring program
 - The lyophilization process
9. FDA recommends that the container closure integrity test be performed in lieu of the sterility test for stability samples at initial time and every 12 months (annually) until expiry.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

IND 000290

EUSA Pharma (USA), Inc.
Attention: Paul Plourde, M.D.
Senior Vice President, Global Medical Oncology
One Summit Square, Suite 201
1717 Langhorne Newtown Road
Langhorne, PA 19047

Dear Dr. Plourde:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "L-asparaginase (*Erwinia chrysanthemi*) [Erwinase]." We also refer to the meeting held on September 3, 2009, between representatives of your firm and the FDA. A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions please contact me at (301) 796-1393.

Sincerely,

{See appended electronic signature page}

Erik Laughner, M.S.
Senior Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosures: FDA Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 3, 2009
TIME: 1:30 PM - 2:30 PM ET
APPLICATION: IND 000290
SPONSOR: EUSA Pharma (US) Inc. [EUSA Pharma]
DRUG NAME: L-asparaginase (*Erwinia chrysanthemi*) [Erwinase]
TYPE OF MEETING: Type B; Face-to-Face
MEETING CHAIR: Jeff Summers
MEETING RECORDER: Erik Laughner
SUBJECT: To discuss the clinical content and format for a BLA application

FDA ATTENDEES:

Patricia Keegan	Director, DBOP/OODP
Joseph Gootenberg	Deputy Director, DBOP/OODP
Jeff Summers	Clinical Team Leader, DBOP/OODP
Patricia Dinndorf	Clinical Reviewer, DBOP/OODP
Erik Laughner	Senior Regulatory Health Project Manager, DBOP/OODP
Gina Davis	Regulatory Project Manager, DBOP/OODP
Vaishali Jarral	Regulatory Project Manager, DBOP/OODP
Hong Zhao	Clinical Pharmacology Team Leader, DCP5/OCF
Jun Yang	Clinical Pharmacology Reviewer, DCP5/OCF
Kyung Lee	Statistical Reviewer, OB/DBV
Anne Pilaro	Supervisory Toxicologist, DBOP/OODP
Michael Orr	Toxicology Reviewer, DBOP/OODP

EUSA PHARMA (EUSA) ATTENDEES:

Tim Corn	Chief Medical Officer
Paul V. Plourde	Senior Vice President
Maggie Filipiak	Director of Regulatory Affairs

(b) (4)

(b) (4)

1.0 MEETING OBJECTIVES:

To discuss the overall content and format of the clinical components for a BLA application

2.0 BACKGROUND:

On May 30, 2006, former IND holder OPi SA and FDA held a pre-BLA meeting to review the status of available CMC, nonclinical, and clinical information on Erwinase for an anticipated future BLA application. At that meeting, FDA indicated that for a BLA

submission, OPI SA could consider a single trial in a limited number of patients hypersensitive to Pegaspargase to determine a dose and schedule of Erwinase that results in depletion of asparagine (pharmacodynamic (PD) endpoint) to a degree similar to that provided by the labeled dose of Pegaspargase in non-hypersensitive patients. Information would be also required on Erwinase pharmacokinetics (PK), immunogenicity. In a July 30, 2008, correspondence, FDA acknowledged EUSA Pharma's submission of data justifying the inherent unreliability of asparagine assay results arising from an inability to control for *ex vivo* metabolism. FDA agreed that asparaginase activity could serve as the primary PK study endpoint which can be reliably measured in the clinical setting and is directly related to asparagine depletion. However, FDA indicated that EUSA Pharma would be expected to document in a future BLA submission all due diligence to collect these samples for PD data to support the review and approval of a BLA.

EUSA Pharma's pivotal open-label COG study AALL07P2 entitled, "Pharmacology and Toxicity of Erwinase Asparaginase Following Allergy to PEG-Asparaginase in the Treatment of Children with Acute Lymphoblastic Leukemia" is well underway. However, EUSA Pharma has archived all samples for measurement of PD, PK, and immunogenicity endpoints until FDA has reviewed the final assay validation reports.

In addition to the ALL0P72 trial, Erwinase is also available to patients through the Erwinase Master Treatment Protocol (EMTP) entitled, "Erwinase (Erwinia L-Asparaginase for Injection) for patients with history of allergic reactions to E coli L-Asparaginase/Pegaspargase who require asparaginase therapy as a component of multi-agent chemotherapy." This protocol will facilitate collection of additional safety data for the planned BLA.

On June 15, 2009, EUSA Pharma requested a clinical pre-BLA meeting to discuss the overall content and submission strategy for a future BLA expected in the first/second quarter of 2010. EUSA Pharma has indicated that a separate CMC specific pre-BLA meeting request would be submitted under separate cover. Draft FDA responses to sponsor questions were communicated to EUSA Pharma on September 1, 2009.

3.0 DISCUSSION

Prior to the actual meeting, EUSA Pharma verbally acknowledged receipt of FDA's comments and provided FDA with the following written agenda and update:

*EUSA Pharma (USA), Inc.
IND 290
Type B (Pre-BLA) Meeting
Sept 3, 2009 1:30pm-2:30pm
AGENDA*

<i>Activity</i>	<i>Time</i>	<i>EUSA Discussion Leader</i>
<i>Question 1: COG CSR toxicity data and laboratory tests</i>	<i>5 min</i>	<i>Paul Plourde</i>
<i>Question 2: COG CSR pharmacokinetics</i>	<i>5 min</i>	<i>Paul Plourde</i>
<i>Question 15 + 6: CRF requirements for COG and compassionate use study</i>	<i>20 min</i>	<i>Paul Plourde</i>
<i>Question 5: Pooled safety data</i>	<i>5 min</i>	<i>Paul Plourde</i>
<i>Question 14 + 20: Datasets (CDISC/PK)</i>	<i>5 min</i>	<i>Paul Plourde</i>
<i>Question 19: Nonclinical reports and literature search</i>	<i>10 min</i>	<i>Paul Plourde</i>
<i>Question 21: QT data summarization</i>	<i>5min</i>	<i>Paul Plourde</i>
<i>Other business</i>	<i>5 min</i>	<i>Paul Plourde</i>

Current status of COG ALL07P2 trial:

- 5 active in Course 1
- 23 completed Course 1
- 9 completed Course 2
- 7 completed Course 3
- 1 completed Course 4
- To date: No deaths, no withdrawals due to AE, 1 SAE still being evaluated

Current status of compassionate use trial (EMTP):

- 675 dosed since 2007; 168 patients enrolled since the beginning of 2009
- 443 CRFs in house (~66%)
- Deaths (n=2; 0.6%)
- Withdrawals due to AE (n=50; 14.8%)
- SAEs (n=63; 18.7%)

SPONSOR SUBMITTED QUESTIONS WITH BACKGROUND AND FDA RESPONSE:

Erwinase[®] has been marketed in the EU for nearly 15 years and the safety and efficacy profile of this product is well characterized. At an FDA meeting in May 2006, the FDA requested a PK/PD bridging clinical study be filed in the BLA in order to obtain approval to market Erwinase[®] in the US. To that end, EUSA filed a PK/PD protocol entitled, “*Pharmacology and Toxicity of Erwinia Asparaginase (Erwinase[®]; Crisantaspase; IND 290) Following Allergy to pegasparaginase in Treatment of Children with Acute Lymphoblastic Leukemia (ALL)*” (abbreviated as COG [Children’s Oncology Group] AALL07P2) in IND 290, amendment 0458. Outside of the COG ALL07P2 trial, Erwinase[®] is made available through the Master Treatment Protocol (EMTP) for compassionate use.

The primary hypothesis of the COG AALL07P2 study is that an appropriate dose and schedule of Erwinase[®] will provide a 48 hour trough asparaginase activity of ≥ 0.1 U/mL in patients with pegasparaginase allergy, similar to that provided by customary doses of the pegasparaginase product. The primary and secondary objectives are listed below:

Primary Objectives of COG AALL07P2

1. To determine if the 48 hour trough serum asparaginase activity is ≥ 0.1 IU/mL.

2. To determine the frequency of asparaginase-related toxicity following Erwinase[®] treatment.
3. To characterize the pharmacokinetics of Erwinase[®] in children with leukemia and allergy to pegasparaginase.

Secondary Objectives of COG AALL07P2

1. To informally compare serum asparaginase activity and plasma asparagine concentration between patients treated with Erwinase[®] on this trial and historical controls treated with pegasparaginase on CCG-1962 and 1961.
2. To determine the 72 hour serum asparaginase activity (Day 8 (pre-dose 4) if the course of Erwinase[®] is started on Monday; Day 13 (pre-dose 6) if the course of Erwinase[®] is started on Wednesday; and Day 11 (predose 5) if the course of Erwinase[®] is started on Friday).
3. To determine the presence of anti-*Erwinia* asparaginase antibodies in children treated with a course(s) of Erwinase[®] following clinical allergy to pegasparaginase (PEG, pegasparaginase).
4. To determine if plasma asparagine is adequately depleted (Day 12 (pre-dose 6) if the course of Erwinase[®] is started on Monday; Day 13 (pre-dose 6) if the course of Erwinase[®] is started on Wednesday or Friday) in a subset of patients.

Children who develop a hypersensitivity to E. coli derived asparaginase often do so after the 2nd or 3rd dose. Therefore, many of the children will continue to receive cyclic courses of Erwinase[®] for possibly as long as 6 months before the completion of their consolidation treatment phase. The primary end point is determined within the first 2 weeks of starting Erwinase[®] treatment. EUSA Pharma is proposing to have data base lock when the last patient (Pt #50) completes the primary endpoint assessment (2 wks after initiating treatment). This is anticipated to be December 31st, 2009. The BLA for Erwinase[®] is planned to be filed in April 2010. A snapshot will be taken of the data up to and including 31 December 2009 and this database will be cleaned. Edit checks will be run across all CRFs resulting in query generation and distribution to the sites. All queries will be resolved on the snapshot before analysis and reporting are undertaken.

In the BLA, the CSR for the COG study will include all visit data collected on or before the data cutoff date. As currently projected, 35/50 (70%) subjects will have completed the trial and will no longer continue to receive Erwinase[®]. These patients will have completed all primary and secondary assessments. Approximately 15/50 (30%) subjects will have completed the primary asparaginase endpoint, but will not have completed the trial at the time of the data cutoff. Note that case report forms for the ongoing COG ALL07P2 trial are collected and entered into the database on a rolling basis, thus for the 15/50 active subjects, many subjects will have more than just the primary endpoint data, but the amount of data included beyond the primary endpoint will vary by subject.

When all patients have completed the study, the sponsor will submit the final CSR post approval.

1. Is the current plan acceptable?

FDA Preliminary Response Provided on September 1, 2009: The plan to submit a BLA supported by a CSR with data on the primary endpoint (asparaginase activity Day 11- 13 of a course of Erwinase) available for 50 patients is acceptable. However, the CSR should at a minimum include complete toxicity data including the results of the “special research laboratory tests” required prior to dose 1 and after dose 6 of the initial course (end of induction phase report) of Erwinase on all 50 patients.

Discussion During the Meeting: EUSA Pharma acknowledged FDA’s draft responses and agreed that all requested data would be provided in the BLA submission for 50 patients through course 1. Any additional data beyond course 1 would also be included.

2. Based on the plan presented, does the FDA concur that there are no deficiencies in the clinical program and that the clinical program is adequate to support product registration?

FDA Preliminary Response Provided on September 1, 2009: The adequacy of the clinical program to support product registration will depend on the quality and the completeness of the data submitted to support the primary study endpoints. Specifically, the application will require complete data in 50 patients for 48 hour trough serum asparaginase activity, at a minimum, complete asparaginase-related toxicity data for 50 patients during the initial course of Erwinase, and adequate data to accurately describe Erwinase pharmacokinetics in children.

The final CSR may be submitted as a post marketing requirement (PMR) to further characterize product safety after all patients have completed therapy.

Discussion During the Meeting: EUSA Pharma acknowledged FDA’s draft responses. EUSA noted that the 12 PK sampling time points were acquired at different times for each patient and that the data would be provided as descriptive statistics and would not avail itself to modeling. FDA acknowledged and clarified that as the study contained a minimal 50 patients for efficacy, missing data points should be kept to an absolute minimum. EUSA agreed.

120 Day Safety Update

The safety of Erwinase® is well established in the literature and will be further assessed in one controlled clinical trial (COG ALL07P2) and as part of the EMTP. Complete safety data analyses from the COG ALL07P2 trial will be provided as part of the full clinical study report (CSR) to be submitted when all patients complete their full course of treatment. Since this will be the only additional safety information and the majority of the data from the COG ALL07P2 trial will be included in the initial BLA, EUSA is not planning on providing a 4 month safety update. EMTP safety information will continue to be summarized in the annual report.

3. Is this plan acceptable to the Agency?

FDA Preliminary Response Provided on September 1, 2009: This plan is acceptable as long as the BLA includes toxicity data on all 50 patients for the first course of Erwinase therapy.

Discussion During the Meeting: EUSA Pharma acknowledged FDA's draft responses. There was no further discussion.

Efficacy

As agreed at the meeting in 28 June 2006, one pivotal study (COG AALL07P2) is being conducted to demonstrate the clinical effectiveness of Erwinase[®] to raise asparaginase to pharmacological levels and to enhance the safety database of Erwinase[®]. As such, EUSA proposes to describe the results from the COG ALL07P2 protocol and efficacy information from the literature in 2.7.3 Summary of Clinical Efficacy and omit 5.3.5.3 ISE from the BLA application. No pooling of data will be done to demonstrate the effectiveness of Erwinase[®].

4. Does the FDA agree that this proposal is acceptable?

FDA Preliminary Response Provided on September 1, 2009: This is acceptable.

Discussion During the Meeting: EUSA Pharma acknowledged FDA's draft responses. There was no further discussion.

Safety

The COG ALL07P2 and the EMTP study provide uncontrolled evidence of the safety of Erwinase[®]. EUSA proposes to summarize the results of the COG ALL07P2 study, safety information from the literature, safety information from the EU studies (summary of the Periodic Safety Update Reports) and safety results from the EMTP study in 2.7.4 Summary of Clinical Safety and omit 5.3.5.3 ISS from the BLA application. No pooling of data will be done to demonstrate the safety of Erwinase[®].

5. Does the FDA agree that this proposal is acceptable?

FDA Preliminary Response Provided on September 1, 2009: No. The application should include a pooled analysis of the COG ALL07P2 study and the EMTP study. Please provide information as to how many patients have received Erwinase through the EMTP and how many completed data forms have been submitted.

Discussion During the Meeting: EUSA Pharma expressed concern regarding pooling of data from uncontrolled (EMTP) and controlled (COG ALL07P2) studies and suggested that the analysis be performed separately. FDA clarified that it was acceptable to analyze data separately; however, pooled datasets and analyses were also needed for the BLA.

EUSA proposes to include in the BLA a synopsis of the Erwinase[®] Master Treatment Protocol (EMTP) study, which will summarize all available safety data through December 31st, 2009. Note that all available safety information for this study will also be submitted in the annual report scheduled to be filed in March of 2010, just prior to the submission of the BLA. An example of the synopsis will be provided in the briefing document.

6. Does the FDA agree that the proposal to submit a synopsis for the EMTP is acceptable?

FDA Preliminary Response Provided on September 1, 2009: It is acceptable to submit a synopsis of the EMTP study. The report of the EMTP study must also include xpt datasets to include the information collected on the EMTP on the "Patient Registration Form," "Drug Accountability Log" and the "Case Report Forms."

Discussion During the Meeting: See discussion captured under question 15.

7. Does the FDA agree that a synopsis of the EMTP study is adequate to summarize the results of the EMTP study in the BLA?

FDA Preliminary Response Provided on September 1, 2009: A synopsis of the EMTP study may be adequate to support the BLA depending on the quality and completeness of the report.

Discussion During the Meeting: EUSA Pharma acknowledged FDA's draft responses. There was no further discussion.

In correspondence dated 02 March 2007 and 06 November 2007, the Agency encouraged the development and validation of methods to measure neutralizing, IgG and IgE antibodies. EUSA will also provide all the data regarding the neutralizing, IgG and IgE antibodies on the patients who finished Erwinase[®] treatment and those who continue in the COG ALL07P2 protocol.

8. Is the above plan acceptable?

FDA Preliminary Response Provided on September 1, 2009: This is acceptable.

Discussion During the Meeting: EUSA Pharma acknowledged FDA's draft responses. There was no further discussion.

Labeling

A proposed draft label is provided in Appendix 1. The proposed indication for Erwinase[®] follows.

ERWINASE[®] (*Erwinia* L-asparaginase) is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with:

- Acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to (b) (4) (b) (4) *E. coli* derived asparaginase.

(b) (4)

9. Does the Agency agree with the proposed indication?

FDA Preliminary Response Provided on September 1, 2009: No. FDA does not find the proposed indication acceptable and suggests an indication similar to the following: Erwinase® is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia and hypersensitivity to

(b) (4)

(b) (4)

Discussion During the Meeting: EUSA Pharma acknowledged FDA's draft responses. There was no further discussion.

Administration

EUSA proposes the following administration for Erwinase®:

- 25,000 IU/m² IM three times a week for two weeks for every course of asparaginase treatment

(b) (4)

- For IV administration, give over a period of 1 to 2 hours in 0.9%NaCl solution through an infusion that is already running or IV push over 3-5 minutes
- The contents of each vial should be reconstituted for injection and should be administered within 15 minutes of reconstitution
- If a delay of more than 15 minutes between reconstitution and administration is unavoidable, the solution should be withdrawn, using a sterile technique, into a sterile glass or polypropylene syringe for the period of the delay
- If the solution has not been used within 8 hours, it should be discarded
- Do not mix other medications with ERWINASE®

10. Does the Agency agree with the proposed administration?

FDA Preliminary Response Provided on September 1, 2009: In order to include

(b) (4)

Discussion During the Meeting: EUSA Pharma acknowledged FDA's draft responses. There was no further discussion.

Procedural/Regulatory

EUSA has submitted the overall BLA table of contents for the Agency's review and comment as Appendix 2.

11. Does the Agency agree that the overall format and content of the eCTD are acceptable?

FDA Preliminary Response Provided on September 1, 2009: This is acceptable.

Discussion During the Meeting: EUSA Pharma acknowledged FDA's draft responses. There was no further discussion.

12. Are there any reports that appear to be missing or need to be moved to another location within the CTD structure?

FDA Preliminary Response Provided on September 1, 2009: No missing or misplaced items were identified. Sections of the application that are supported by a series of literature references must also contain an integrated report based on the literature, not just the individual papers.

Discussion During the Meeting: EUSA Pharma acknowledged FDA's draft responses. There was no further discussion.

Priority Review

Because Erwinase[®] is a safe and effective therapy where no satisfactory alternative therapy exists, EUSA will be requesting a priority review in the initial BLA.

13. Although priority review designation is not granted until the application has been filed, does the Agency agree that this application satisfies the criteria to receive the priority review designation?

FDA Preliminary Response Provided on September 1, 2009: The BLA may be considered for priority review. However, the final determination of status will be made when the BLA is submitted.

Discussion During the Meeting: EUSA Pharma acknowledged FDA's draft responses. There was no further discussion.

CDISC Data Set Format

At the time the BLA is filed, EUSA plans on submitting datasets in legacy format for the COG ALL07P2 PK/PD study. No other datasets will be submitted in the BLA.

14. Does the Agency require any additional clinical study-specific datasets to be submitted to support the BLA?

FDA Preliminary Response Provided on September 1, 2009: No. Datasets in the legacy format of the COG are not acceptable. The agency strongly encourages that data be supplied in CDISC format in order to facilitate a timely review. Appendix 1 contains a summary of important components of CDISC compliant datasets. If EUSA Pharma does not choose to submit the datasets in CDISC format, appendix 1 includes a summary of the requirements for acceptable datasets to support an application.

Discussion During the Meeting: EUSA Pharma acknowledged FDA comments and agreed that additional resources would be utilized in order to comply with this request, while at the same time maintaining the current timeline for BLA submission. The need for additional resources may be recuperated in a modified cost recovery request.

Case Report Forms

Case report forms (CRFs) for patients who died or discontinued due to an adverse event will be included in the BLA for the COG ALL07P2 study.

15. Are there any other categories for which the Agency would like to see CRFs submitted?

FDA Preliminary Response Provided on September 1, 2009: Complete CRFs from all patients from the ALL07P2 study should be submitted. The "Patient Registration Form," "Drug Accountability Log" and the "Case Report Forms" for all subjects enrolled on the EMTP study should also be submitted.

Discussion During the Meeting: EUSA Pharma noted that there were different dosing regimens, patient characteristics, and data collection procedures between the COG study and EMTP. For the EMTP, the data was currently only available in paper form and the data entry as proposed by FDA could be very laborious, costly, and possible delay the BLA submission. FDA acknowledged the concerns, but stated that all EMTP study data captured on the CRF should be submitted as xpt data sets. All CRFs for both ALL07P2 and EMTP should be submitted in the BLA for review as FDA evaluates the quality of the database by cross-checking the CRFs with the dataset values. The CRFs were critical for safety evaluation. FDA noted that the EMTP CRF was specifically designed with the Division's assistance for this very purpose. FDA noted that EUSA Pharma could reconsider this extra cost in the IND charging request renewal. EUSA acknowledged the issue and agreed that this information would be provided in the BLA submission.

(b) (4)

16. Does the Agency agree with the above plan (b) (4)
(b) (4)

FDA Preliminary Response Provided on September 1, 2009: As Erwinase has been designated as an Orphan drug product, further study in pediatric populations for treatment of ALL is not required under the Pediatric Research Equity Act (PREA).

Discussion During the Meeting: EUSA Pharma acknowledged FDA's draft responses. There was no further discussion.

17. Having executed the program that will be filed in the BLA (COG ALL07P2 and EMTP) in children does Erwinase[®] qualify for pediatric exclusivity?

FDA Preliminary Response Provided on September 1, 2009: Pediatric exclusivity status does not apply to biologics at this time.

Discussion During the Meeting: EUSA Pharma acknowledged FDA's draft responses. There was no further discussion.

REMS

Erwinase[®] has been marketed in EU for nearly 15 years and the safety profile of this product is well characterized. The safety profile of the class of L-asparaginases has revealed serious allergic reactions, pancreatitis, glucose intolerance, and coagulopathy (hemorrhage and thrombosis) adverse events. Because the efficacy of Erwinase[®] has been established and the safety profile of Erwinase[®] is well understood, EUSA does not intend to submit a REMS in the BLA.

18. Does the Agency agree that a REMS is not needed for Erwinase[®]?

FDA Preliminary Response Provided on September 1, 2009: The Division agrees that a REMS is not needed

Discussion During the Meeting: EUSA Pharma acknowledged FDA's draft responses. There was no further discussion.

Preclinical

A list of literature used to support the safety of Erwinase[®] was submitted as part of the previous meeting held on 20 May 2006 and is listed in Appendix 3. EUSA proposes to include this list of literature and any additional literature published on Erwinase[®] from May 2006 to December 2009 in the BLA.

19. Is this plan acceptable to the Agency?

FDA Preliminary Response Provided on September 1, 2009: No. In the BLA submission, provide the final study reports for all nonclinical studies used to support the

approval of Erwinase[®] in Europe. In addition to these reports, provide the PDF files of the original articles used to support the safety of Erwinase[®], and an integrated summary of the reported pharmacology and toxicology findings (i.e. both literature, and from any available nonclinical study reports) in Module 2 of the eCTD BLA.

Discussion During the Meeting: EUSA Pharma noted that as this was a very old IND with multiple sponsors over the years, all the nonclinical reports may not be available. FDA acknowledged this difficulty and clarified that the reproductive toxicology and long term exposure data reports were the most important for review. EUSA indicated that a search for all nonclinical reports has thus far found 9 completed study reports. EUSA would continue to search for any old reports, many of which were probably produced on a typewriter and would require scanning into PDFs and incorporation of document navigation links.

FDA clarified that it would be acceptable to conduct a literature search on Erwinase and not other asparaginases. This literature search should be comprehensive and discussed in Module 2 of the BLA.

ADDITIONAL FDA COMMENTS:

Statistical/Clinical Pharmacology

20. In addition to summary tables, please provide demographic information including age, body weight, BSA, actual dose together with the individual's PK, PD and immunogenicity raw data using SAS transport file (*.xpt). In addition, any concentrations and/or subjects that are excluded from the analysis should be flagged and maintained in the datasets. The SAS programs that are used to create the derived datasets for the efficacy endpoints (PK, PD and immunogenicity data) and the SAS programs that are used for efficacy data (PK, PD and immunogenicity data) analyses should be included in the BLA submission.

Discussion During the Meeting: EUSA Pharma acknowledged FDA's draft responses and agreed to provide the requested information. FDA clarified that gender/race data should also be provided.

21. With regard to QT assessment, EUSA Pharma should report the number and percentage of patients with a QTc interval increase ≥ 500 ms and a change ≥ 60 ms from baseline in addition to the routine analysis. EUSA Pharma should also report clinically relevant changes in other ECG measurements (PR, QRS, T wave amplitude) and waveform morphology.

Discussion During the Meeting: EUSA Pharma agreed to provide the requested information, although it may be difficult to interpret because of multiple confounding factors. FDA acknowledged.

Clinical

22. See Appendix 1 for additional information that will facilitate the construction of an acceptable BLA submission.

Discussion During the Meeting: EUSA Pharma acknowledged FDA's draft responses. There was no further discussion.

ADDITIONAL DISCUSSION:

FDA noted that should EUSA Pharma need to revise their recently submitted cost recovery request to take into account the additional resources needed to meet FDA's data expectations for a BLA, a new cost recovery request should be submitted and the current one formally withdrawn. EUSA Pharma acknowledged.

EUSA Pharma noted that the CMC pre-BLA meeting was anticipated to occur later in Q4 2009, contingent on the progress of manufacturing milestones.

Appendix 1

OODP's End-of-Phase 2 General Advice for Planned Marketing Applications

NDA and BLA applications must comply with all applicable statutes and regulations (e.g. 21 CFR 314, 21 CFR Part 201, and 21 CFR Parts 600 and 601). In addition, FDA has published many guidance documents (available at www.fda.gov/RegulatoryInformation/Guidances/default.htm) that contain important information necessary for preparing a complete, quality application.

The following comments, based on our experience with other applications, are intended to help you plan and prepare for submitting a quality application. This list is not inclusive of all issues you need to consider in preparing an application, but highlights areas where we have seen problems and/or issues that can delay our timely review of applications. These are general comments; if you believe some are inapplicable to your planned application we encourage you to provide justification and discuss it with us.

Clinical:

- 1) Submit copies of the original versions of all protocols, statistical analysis plans, DSMB and adjudication committee charters, and all amendments.
- 2) Submit copies of minutes of all DSMB, and adjudication committee meetings.
- 3) If investigator instructions were produced in addition to the protocol and investigator brochure, submit copies of all such instructions.
- 4) Submit copies (in SAS transport format) of randomization lists and, if used, IVRS datasets.
- 5) Submit copies (in SAS transport format) of all datasets used to track adjudications.
- 6) Clinical study report(s) should follow the ICH E3 Structure and Content of Clinical Study Reports guidance (www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129456.pdf).
- 7) For each of the completed Phase 3 clinical trials, submit a table with the following columns:
 - a) Site number
 - b) Principal investigator
 - c) Location: City, State, Country
 - d) Number of subjects screened
 - e) Number of subjects randomized
 - f) Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites)
 - g) Number of protocol violations (Major, minor, definition)
- 8) Prepare integrated summaries of safety and effectiveness (ISS/ISE) as required by 21 CFR 314.50 and in conformance with the following guidance documents:
 - a) Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf)
 - b) Cancer Drug and Biological Products-Clinical Data in Marketing Applications (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071323.pdf)
- 9) Provide an assessment of safety as per the Guidance for Industry: Premarketing Risk Assessment (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf).

- 10) Safety Analysis Plan. In conjunction with the Statistical Analysis Plan which generally addresses statistical issues for efficacy, include a Quantitative Safety Analysis Plan (QSAP). The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. At a minimum the Safety Analysis Plan should address the following components:
- a) Study design considerations (See: FDA Guidance to Industry: Premarketing Risk Assessment, (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf).
 - b) Safety endpoints for Adverse Events of Special Interest (AERI)
 - c) Definition of Treatment Emergent Adverse Event (TEAE)
 - d) Expert adjudication process (Expert Clinical Committee Charter or Independent Radiology Review Charter)
 - e) Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)
 - f) Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.
 - g) When unanticipated safety issues are identified the QSAP may be amended.
- 11) Provide detailed information, including a narrative, for all patients terminating study drug or participation in the study prematurely including those categorized as other, lost to follow up, physician decision, or subject decision.
- 12) Narrative summaries should contain the following components:
- a) subject age and gender
 - b) signs and symptoms related to the adverse event being discussed
 - c) an assessment of the relationship of exposure duration to the development of the adverse event
 - d) pertinent medical history
 - e) concomitant medications with start dates relative to the adverse event
 - f) pertinent physical exam findings
 - g) pertinent test results (for example: lab data, ECG data, biopsy data)
 - h) discussion of the diagnosis as supported by available clinical data
 - i) a list of the differential diagnoses, for events without a definitive diagnosis
 - j) treatment provided
 - k) re-challenge results (if performed)
 - l) outcomes and follow-up information
 - m) an informed discussion of the case, allowing a better understanding of what the subject experienced.
- 13) Provide complete CRFs for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events. You should be prepared to supply any additional CRFs upon request.
- 14) For patients listed as discontinued to due “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated. In addition, the verbatim description from the CRF should be included as a variable in the adverse event data set.
- 15) Marketing applications must include certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies, including those at foreign sites, covered by the regulation. This requires that investigators provide information to the sponsor

during the course of the study and after completion. See Guidance for Industry - Financial Disclosure by Clinical Investigators

(www.fda.gov/RegulatoryInformation/Guidances/ucm126832.htm).

- 16) Pediatric Studies. All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is exempt (i.e. orphan designation), waived or deferred. We request that you submit a pediatric plan that describes development of your product to provide important information on the safe and effective use of in the pediatric population where it may be used. If the product will not be used in pediatric populations your application must include a specific waiver request including supporting data. A request for deferral, must include a pediatric plan, certification of the grounds for deferring the assessments, and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time.
- 17) Regulations require that the safety and effectiveness data be presented for subgroups including “by gender, age, and racial subgroups”. Therefore, as you are gathering your data and compiling your application, we request that you include this data and pertinent analysis.
- 18) In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the “TQT” study may be appropriate. Please plan to address this issue early in development.
- 19) The NDA/BLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP) 6010.3 (www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm080121.pdf). To facilitate the review, we request you provide analyses and discussion, where applicable, that will address the items in the template, including:
 - a) Other Relevant Background Information – important regulatory actions in other countries or important information contained in foreign labeling.
 - b) Exposure-Response Relationships – important exposure-response assessments.
 - c) Less common adverse events (between 0.1% and 1%).
 - d) Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
 - e) Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
 - f) Marked outliers and dropouts for laboratory abnormalities.
 - g) Analysis of vital signs focused on measures of central tendencies.
 - h) Analysis of vital signs focused on outliers or shifts from normal to abnormal.
 - i) Marked outliers for vital signs and dropouts for vital sign abnormalities.
 - j) A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the “investigations” SOC or in an SOC pertaining to the specific abnormality. For example, all Aes coded as “hyperglycemia” (SOC metabolic) and “low blood glucose” (SOC investigations) should be tabulated. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.
 - k) Overview of ECG testing in the development program, including a brief review of the nonclinical results.
 - l) Standard analyses and explorations of ECG data.
 - m) Overdose experience.
 - n) Analysis and summary of the reasons and patterns of discontinuation of the study drug. Identify for each patient the toxicities that result in study discontinuation or dose reduction.

- o) Explorations for:
 - i) Possible factors associated with a higher likelihood of early study termination; include demographic variables, study site, region, and treatment assignment.
 - ii) Dose dependency for adverse findings
 - iii) Provide summary tables of the incidence of adverse events based on the cumulative dose and the average dose administered.
 - iv) Time dependency for adverse finding
 - v) Provide data summarizing the length of time subjects experience adverse events and whether recovery occurs during treatment.
 - vi) Drug-demographic interactions
 - vii) Drug-disease interactions
 - viii) Drug-drug interactions
- p) Dosing considerations for important drug-drug interactions.
- q) Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

Datasets and Programs:

- 20) The SAS programs that are used to create the derived datasets for the efficacy endpoints and the SAS programs that are used for efficacy data analysis should be included. If the SAS programs use any macro programs, please provide all necessary macro programs.
- 21) Please provide the location of the SAS dataset, the names of the variables used and the programs used to get every value proposed to be included in the label.
- 22) The SAS transport files should be created by a procedure which allows the file to be easily read by the JMP software.
- 23) Data Format:
 - a) *We strongly encourage that data be supplied in CDISC format.* The Clinical Data Interchange Standards Consortium (CDISC) Submission Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) outline the principles for data submission and analysis (www.cdisc.org).
 - i) Study Data Tabulation Model (SDTM) Issues:
 - (1) The current published SDTM and SDTM Implementation Guide (SDTMIG) should be followed carefully. Refer to the SDTMIG section on Conformance (3.2.3)
 - (2) Domains
 - (3) There are additional domains listed below that are not included in the current DTMIG. Information on these domains may be obtained at www.cdisc.org and are expected to be published in the next versions of SDTM and SDTMIG (Version 3.1.2). If applicable, please use these domains.
 - (a) (DV) Protocol deviations
 - (b) (DA) Drug Accountability
 - (c) (PC, PP) Pharmacokinetics
 - (d) (MB, MS) Microbiology
 - (e) (CF) Clinical Findings
 - (4) The following domains are not available with SDTM but may be included if modeled following the principles of existing SDTM domains.
 - (a) Tumor information
 - (b) Imaging Data
 - (c) Complex Inclusion/Exclusion Criteria
 - (5) Variables
 - (a) All required variables are to be included.
 - (b) All expected variables should be included in all SDTM datasets.

- (c) Variables (expected or permissible) for which no values will be submitted should be explicitly stated and discussed with the review division.
 - (d) A list of all Permissible variables that will be included and those that will not be included for each domain should be provided for review and discussed with the review division.
 - (e) A list and description of all variables that will be included in the Supplemental Qualifier dataset should be provided.
 - (f) Do not include any variables in the SDTM datasets that are not specified in the SDTMIG.
- (6) Specific issues of note:
- (a) SDTM formatted datasets should not provide replication of core variables (such as treatment arm) across all datasets.
 - (b) Only MedDRA preferred term and system organ class variables are allowed in the AE domain. However, the other levels of the MedDRA hierarchy should be placed in the SUPQUAL dataset or an ADaM dataset.
 - (c) These issues can be addressed through the request for ADaM datasets
- ii) Analysis Data Model (ADaM) Issues:
- (1) Specify which ADaM datasets you intend to submit.
 - (2) Include a list of all variables (including sponsor defined or derived) that will be included in the ADaM datasets.
 - (3) Discuss the structure of the datasets with the reviewing division and specify in the QSAP.
 - (4) Within each adverse event analysis dataset, please include all levels of the MedDRA hierarchy as well as verbatim term.
 - (5) Indicate which core variables will be replicated across the different datasets, if any.
 - (6) SDTM and ADaM datasets should use the unique subject ID (USUBJID). Each unique subject identifier should be retained across the entire submission.
- iii) General Items:
- (1) Controlled terminology issue:
 - (a) Use a single version of MedDRA for a submission. Does not have to be the most recent version
 - (b) We recommend that the WHO drug dictionary be used for concomitant medications.
 - (c) Refer to the CDISC terminology for lab test names.
 - (d) Issues regarding ranges for laboratory measurements should be addressed.
 - (2) Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the division which studies are most appropriate for integration.
 - (3) Perform the following SMQ's on the ISS adverse event data and include the results in your ISS report: 1. Severe cutaneous adverse reactions SMQ and 2. Possible drug related hepatic disorders – comprehensive search SMQ. Also, provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.
- b) If you submit **non-CDISC Datasets**, we request the following:
- i) All datasets should contain the following variables/fields (in the same format and coding)
 - (1) Each subject should have one unique ID across the entire NDA
 - (2) Study number
 - (3) Treatment assignment
 - (4) Demographic characteristics (age, race, gender, etc.)
 - ii) The safety dataset that should include the following fields/variables:

- (1) A unique patient identifier
 - (2) Study/protocol number
 - (3) Patient's treatment assignment
 - (4) Demographic characteristics, including gender, chronological age (not date of birth), and race
 - (5) Dosing at time of adverse event
 - (6) Dosing prior to event (if different)
 - (7) Start and stop dates for adverse events
 - (8) Days on study drug at time of event
 - (9) Outcome of event (e.g. ongoing, resolved, led to discontinuation)
 - (10) Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).
 - (11) Marker for serious adverse events
 - (12) Verbatim term
- iii) The adverse event dataset should include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset should also include the Verbatim term taken from the case report form. Ensure that mapping of a preferred term to the primary MSSO defined SOC level is not changed.
 - iv) See the attached mock adverse event data set in Figure 1 that provides an example of how the MedDRA variables should appear in the data set. Note that this example only pertains to how the MedDRA variables should appear and does not address other content that is usually contained in the adverse event data set.
 - v) In the adverse event data set, please provide a variable that gives the numeric MedDRA code for each lower level term.
 - vi) The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire NDA. If this is not an option, then, at a minimum, it is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.
 - vii) Provide a detailed description for how verbatim terms were coded to lower level terms according to the ICH MedDRA Term Selection: Points to Consider document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.
 - viii) The spelling and capitalization of MedDRA terms should match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.
 - ix) The concomitant medication dataset should use the standard nomenclature and spellings from the WHO Drug dictionary and include the numeric code in addition to the ATC code/decode.
 - x) Ensure that laboratory data are organized in the data sets in a standardized manner with consistent units and a single reference range for each laboratory variable. Include a variable that indicates whether the lab result was from the local lab or central lab. Also, the variable for the laboratory result should be in numeric format. Define the range(s), with supporting documentation, that are used to identify severe toxicity.
 - xi) Perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.

- xii) In every dataset, all dates should be formatted as ISO date format.
- xiii) Across all datasets, the same coding should be used for common variables, e.g. "PBO" for the placebo group. Datasets should not incorporate different designations for the same variable, e.g. "PBO" in one dataset, and "0 mg" or "Placebo," in another datasets. If the coding cannot be reconciled, another column using a common terminology for that variable should be included in the datasets.
- xiv) A single combined analysis dataset including variables from a number of separate data sets can sometimes be useful to the medical review officer and may avoid data set errors caused by joining these variables together using JMP. Provide a dataset (SAS Transport file), including one record per subject screened, that includes the following variables
 - (1) Study Information: Subject ID, subject enrolled (Y/N), subject in efficacy population (Y/N), subject in safety population (Y/N), intent-to-treat population (Y/N), per-protocol population (Y/N), evaluable patient population (Y/N), date/time of randomization and date of the first study treatment, etc.
 - (2) Demographics: Sex, race/ethnicity, age, weight, BMI, location U.S. (Y/N), region (e.g., North America, Eastern Europe, Western Europe, etc.)
 - (3) Study Medications: Treatment assignment (for efficacy analyses), treatment designation for safety analyses ("as treated"), date/time of initial dose, date/time of last dose, total days of treatment, total dose received. In addition, provide the study medication lot numbers used for each dose administered.
 - (4) Baseline Disease Characteristics: e.g. Performance status, previous treatment regimens or procedures, and other prognostic factors as deemed necessary
 - (5) Non-protocol specified anti-cancer therapy (systemic medication/surgery/radiotherapy, etc) : e.g. indicators for such procedures, date of such procedures and type or reasons for the procedures, etc
 - (6) Outcomes: For time-to-event type of endpoints, please provide for each subject the censoring status, the time-to-event, the date of the event and which event type occurred (when an event occurs), the reasons for censoring if censored and the data-cut-off date. Information for individual component of the primary endpoint should also be provided. The variables used for sensitivity analyses for the primary and key secondary efficacy endpoints should be included. The important time variables, usually used for deriving variables for sensitivity analyses, such as the last disease assessment time, last disease assessment time before > 1 missing assessment, last assessment time prior to non-protocol specified anti-cancer therapy and last contact time, etc., should be included. For laboratory results include a variable that indicates whether the lab result was from the local lab or central lab. Also, the variable for the laboratory result should be in numeric format. Define the range(s), with supporting documentation, that are used to identify severe toxicity
 - (7) Necessary data documentation, for example, algorithm for variable derivation, source of the data (i.e. corresponding CRF pages), decoding of the data values (i.e. data format), indication of data structure (one record per subject or one record per visit per subject), etc., should be included
 - (8) Other: Please provide a Y/N variable for potential conflict of interest, i.e., subjects enrolled at sites where an investigator has reported a potential conflict of interest(s) should receive a "yes" flag

Physician's Labeling:

24) Highlights:

- a) Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]
- b) The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
- c) The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]
- d) The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]
- e) The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to 21 CFR 201.57(a)(4) and to www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom).
- f) For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance]. Recent major changes apply to only 5 sections (Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions).
- g) The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:
 "(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."
- h) Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.
- i) Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
- j) A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)].
- k) Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights.
- l) The Patient Counseling Information statement must appear in Highlights and must read "See 17 for PATIENT COUNSELING INFORMATION." [See 21 CFR 201.57(a)(14)]
- m) A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.
- n) A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

25) Table of Contents:

- a) The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]
- b) The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
- c) Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.

- d) Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
- e) When a subsection is omitted, the numbering does not change [see 21 CFR 201.56(d)(1)]. For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (*not 8.2*)
 - 8.4 Pediatric Use (*not 8.3*)
 - 8.5 Geriatric Use (*not 8.4*)
- f) When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents:

“*Sections or subsections omitted from the Full Prescribing Information are not listed.”

26) Full Prescribing Information (FPI):

- a) Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
- b) Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline.
- c) Do not refer to adverse reactions as “adverse events.” Please refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format” (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf).
- d) The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [see Use in Specific Populations (8.4)] not See Pediatric Use (8.4). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf>]
- e) Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
- f) Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]
- g) The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.
- h) There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.
- i) The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.

- j) If the “Rx only” statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.
- k) Refer to www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format.
- l) Refer to the Institute of Safe Medication Practices’ website (<http://www.ismp.org/Tools/abbreviationslist.pdf>) for a list of error-prone abbreviations, symbols, and dose designations.

Electronic Common Technical Document (eCTD):

27) Relating sequences properly allows reviewers to easily navigate the application’s original and supplemental submissions. By relating sequences correctly a reviewer can focus on the data at hand without wondering “what is missing” or “what are the reasons for this disorganized submission?” Delays in your review are also avoided.

- a) First-level submission types should not use related sequence
 - i) First-level submission types are
 - (1) “original-application”
 - (2) "annual-report"
 - (3) "efficacy-supplement"
 - (4) "labeling-supplement"
 - (5) "chemistry-manufacturing-controls-supplement"
 - (6) "other"
 - b) Second-level submission types should use a single related sequence
 - i) The related sequence should always be a first-level submission type
 - ii) Second-level submission types are:
 - (1) "amendment"
 - (2) "resubmission"
 - iii) Related Sequences are indicated in the us-regional.xml file:

Submission Type	Level	Related Sequence
Original	Primary	NO
Annual Report	Primary	NO
Efficacy Supplement	Primary	NO
Labeling Supplement	Primary	NO
CMC Supplement	Primary	NO
Other	Primary	NO
Amendment	Secondary	YES
Resubmission	Secondary	YES

- c) See Appendix 1 for examples of correct usregional.xml file submission code. Contact ESUB@fda.hhs.gov with any questions.

Other Issues:

- 28) The application should include a statement that the manufacturing facilities are ready for inspection upon FDA receipt of the application.
- 29) The application should contain a table that list all of the manufacturing facilities (e.g. drug product, drug substance, packaging, control/testing), including name of facility, full address including street, city, state, country, FEI number for facility (if previously registered with FDA), full name and title,

telephone, fax number and email for on-site contact person, the manufacturing responsibility and function for each facility, and DMF number (if applicable).

- 30) Review of an application can be facilitated by including a chronology of prior substantive communications with FDA and copies of official meeting/telecon minutes.

Figure 1:

Please note that the HLGT and HLT level terms in this table are from the primary MedDRA mapping only. There is no need to provide HLT or HLGT terms for any secondary mappings. This mock table is intended to address content regarding MedDRA, and not necessarily other data that is typically found in an adverse event data set.

Unique Subject Identifier (USUBJID)	Sequence Number (AESEQ)	Study Site Identifier (SITEID)	Unique Subject Identifier	Coding Dictionary Information	Reported Term for AE (Verbatim)	Lower Level Term MedDRA Code	Lower Level Term (LLT)	Preferred Term High Level Term (HLT)	High Level Group Term (HLGT)	System Organ Class (SOC)	Secondary System Organ Class 2 (SOC2)	Secondary System Organ Class 3 (SOC3)	Secondary System Organ Class 4 (SOC4)
01-701-1015	1	701	1015	MedDRA version 8.0	redness around application site	10003058	Application site redness	Application site redness	Administration site reactions	General disorders and administration site conditions	Skin and subcutaneous tissue disorders		

Appendix 1. Code snippet examples of correct usregional.xml file submissions:

An usregional.xml file for a First Level Submission

NOTE because this is a primary submission type there is NO related sequence:

```
<?xml version="1.0" standalone="no"?>
<?xml-stylesheet type="text/xsl" href="../../util/style/us-regional.xsl" ?>
<!DOCTYPE fda-regional:fda-regional SYSTEM "../../util/dtd/us-regional-v2-01.dtd">
<fda-regional:fda-regional xmlns:fda-regional="http://www.ich.org/fda"
xmlns:xlink="http://www.w3c.org/1999/xlink" dtd-version="2.01">
  <admin>
    <applicant-info>
      <company-name> Pharma USA</company-name>
      <date-of-submission>
        <date format="yyyymmdd">20080601</date>
      </date-of-submission>
    </applicant-info>
    <product-description>
      <application-number>999999</application-number>
      <prod-name type="established">Fixitol</prod-name>
    </product-description>
    <application-information application-type="nda">
      <submission submission-type="labeling supplement">
        <sequence-number>0010</sequence-number>
      </submission>
    </application-information>
  </admin>
```

In the example above the sponsor is sending in a labeling supplement and it will not have a related sequence.

In the example below the sponsor has been asked to provide some additional data to support their labeling supplement. Because it is an amendment it will need to designate a related sequence.

```
<?xml version="1.0" standalone="no"?>
<?xml-stylesheet type="text/xsl" href="../../util/style/us-regional.xsl" ?>
<!DOCTYPE fda-regional:fda-regional SYSTEM "../../util/dtd/us-regional-v2-01.dtd">
<fda-regional:fda-regional xmlns:fda-regional="http://www.ich.org/fda"
xmlns:xlink="http://www.w3c.org/1999/xlink" dtd-version="2.01">
  <admin>
    <applicant-info>
      <company-name> Pharma USA</company-name>
      <date-of-submission>
        <date format="yyyymmdd">20080705</date>
      </date-of-submission>
    </applicant-info>
    <product-description>
      <application-number>999999</application-number>
      <prod-name type="established">Fixitol</prod-name>
    </product-description>
    <application-information application-type="nda">
      <submission submission-type="amendment">
        <sequence-number>0012</sequence-number>
        <related-sequence-number>0010</related-sequence-number>
      </submission>
    </application-information>
  </admin>
```

