DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125359/0

BLA APPROVAL

November 18, 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 (BLA) dated October 29, 2010, received November 1, 2010, submitted under section 351 of the Public Health Service Act for ERWINAZE (asparaginase *Erwinia chrysanthemi*) and to our approval letter dated November 18, 2011. That letter contained an error in the reporting date under postmarketing commitment number 8. This replacement letter contains the correct reporting date. The effective date of the action has not changed and will remain November 18, 2011, the date of the original action letter.

We acknowledge receipt of all subsequent amendments received through November 16, 2011.

We have approved your BLA for asparaginase *Erwinia chrysanthemi* effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, asparaginase *Erwinia chrysanthemi*, under your existing Department of Health and Human Services U.S. License No. 1829. Asparaginase *Erwinia chrysanthemi* 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 *E. coli*-derived asparaginase.

Under this license, you are approved to manufacture asparaginase *Erwinia chrysanthemi* drug substance at (b) (4) The final formulated product will be manufactured and filled a (b) (4) and labeled and packaged at (b) (4) You may label your product with the proprietary name ERWINAZE and market it in a carton of 5 vials; each single vial contains 10,000 International Units of asparaginase *Erwinia chrysanthemi.*

The dating period for asparaginase *Erwinia chrysanthemi* shall be 24 months from the date of manufacture when stored at 2-8 °C. The date of drug product manufacture shall be defined as (b) (4). The dating period for your drug substance shall be (b) (4) from (b) (4) Results of

ongoing stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

You are not currently required to submit samples of future lots of asparaginase *Erwinia chrysanthemi* to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of asparaginase *Erwinia chrysanthemi*, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

ADVISORY COMMITTEE

Your application for asparaginase *Erwinia chrysanthemi* was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

CONTENT OF LABELING

We are approving this application for use as recommended in the enclosed agreed-upon labeling text.

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. For administrative purposes, please designate this submission "**Product Correspondence – Final SPL for approved BLA STN 125359/0**."

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels and carton and immediate container labels submitted on November 14, 2011 as soon as they are available, but no more than 30 days after they are printed. Please

submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved BLA STN 125359/0**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

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 this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of embryo-fetal toxicity or anti-drug antibody responses.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA is not yet sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1. To conduct non-clinical embryo-fetal development and toxicity (EFT; ICH S5(R2) Harmonized Segment C) studies of ERWINAZE in rats and rabbits.

   The timetable you submitted on November 14, 2011, states that you will conduct this study according to the following schedule:

   Final Protocol Submission: February 2012

Final Report Submission: December 2012

2. To conduct non-clinical fertility and early pregnancy (Segment I; ICH S5(R2) Harmonized Segment A-B) studies of ERWINAZE in rats.

   The timetable you submitted on November 14, 2011, states that you will conduct this study according to the following schedule:

   Final Protocol Submission: April 2012
   Final Report Submission: February 2013

3. To conduct non-clinical peri-postnatal developmental (PPND; Segment III; ISC S5(R2) Harmonized Segment D-F) studies of ERWINAZE in rats.

   The timetable you submitted on November 14, 2011, states that you will conduct this study according to the following schedule:

   Final Protocol Submission: September 2012
   Final Report Submission: November 2013

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.

   The timetable you submitted on November 14, 2011, states that you will conduct this study according to the following schedule:

   Final report submission: October 2012

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.

   The timetable you submitted on November 14, 2011, states that you will conduct this study according to the following schedule:

   Final report submission: October 2012

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of anti-drug antibody responses.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

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.

   The timetable you submitted on November 14, 2011, states that you will conduct this trial according to the following schedule:

   Final report submission: April 2013

Submit protocols to your IND, with a cross-reference letter to this BLA. Submit all final reports to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

7. To conduct a container closure integrity study and determine the sensitivity of the test methods.

   The timetable you submitted on November 14, 2011, states that you will conduct this study according to the following schedule:

   Final Report Submission as a CBE-30 supplement: December 2011

8. To conduct performance qualification of the ERWINAZE lyophilization process.

   The timetable you submitted on November 14, 2011, states that you will conduct this study according to the following schedule:

   Final Report Submission as a CBE-30 supplement: March 2012

9. To provide validation data from the executed protocol for shipping ERWINAZE drug product from the (b) (4) to the US market.

   The timetable you submitted on November 14, 2011, states that you will conduct this study according to the following schedule:

   Final Report Submission as a CBE-30 supplement: December 2011

10. To conduct a study to substantiate the use of (b) (4) as the (b) (4).

    The timetable you submitted on November 14, 2011, states that you will conduct this study according to the following schedule:

    Final Report Submission as a CBE-30 supplement: December 2011

11. To collect data from (b) (4) on three lots of thawed and diluted drug substance solution prior to (b) (4). The final validation report should contain a description of the method, the (b) (4) results, and an assessment of the impact of (b) (4) on drug product quality and the drug product manufacturing.

    The timetable you submitted on November 14, 2011, states that you will conduct this study according to the following schedule:

    Final Report Submission as a CBE-0 supplement: June 2012

12. Implement the proposed process improvements described in the March 4, 2011, BLA amendment and re-assess the bioburden and endotoxin limits based on data from three extraction batches.

    The timetable you submitted on November 14, 2011, states that you will conduct this study according to the following schedule:

    Final Report Submission as a CBE-0 supplement: July 2012

13. 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 from three runs, demonstrating that acceptance criteria are met.

    The timetable you submitted on November 14, 2011, states that you will conduct this study according to the following schedule:

    Final Report Submission as a CBE-0 supplement: November 2012

14. To complete the qualification of bioburden and endotoxin in-process test methods: The final reports for the bioburden and endotoxin assay will each provide data on two additional batches of drug substance.

    The timetable you submitted on November 14, 2011, states that you will conduct this study according to the following schedule:

    Final Report Submission as a CBE-0 supplement: July 2012

15. 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 final report of this analysis together with any revised release and stability specifications will be submitted in accordance with 21 CFR 601.12.

    The timetable you submitted on November 14, 2011, states that you will conduct this study according to the following schedule:

    Final Report Submission: October 2013

16. 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 together with any revisions in the established hold times will be submitted in accordance with 21 CFR 601.12.

The timetable you submitted on November 14, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission: December 2013

17. To increase the assay sensitivity for SDS-PAGE. The revised assay will be submitted together with the validation report and supporting test results.

The timetable you submitted on November 14, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission as a CBE-30 supplement: December 2013

18. 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 together with any revisions to your control strategy will be submitted as a final report in accordance with 21 CFR 601.12.

The timetable you submitted on November 14, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission: March 2012

19. To provide a revised protocol for qualification of the current and future ERWINAZE reference standards.

The timetable you submitted on November 14, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission as a prior approval supplement: December 2011

20. To submit an experimental plan for evaluating and, if appropriate, implementing L-asparagine as the substrate for measuring the K_m and k_{cat} of ERWINAZE DS and DP.

The timetable you submitted on November 14, 2011, states that you will conduct this study according to the following schedule:

Final Plan Submission: December 2011

21. To provide an experimental plan to assess the types and amounts of smaller sub-visible particulates (b) (4) in the final drug product under real-time and stress stability conditions along with a timetable for this work. The plan and a timescale for the subsequent assessment of the impact sub-visible particles may have on the quality, clinical safety and efficacy of ERWINAZE DP along with a control strategy will be provided in accordance with 21 CFR 601.12.

The timetable you submitted on November 14, 2011, states that you will conduct this study according to the following schedule:

Final Plan Submission: December 2011

22. To revise the [redacted] (b) (4) used for DS and DP release testing in order to enable chromatographic base-line resolution of most [redacted] (b) (4) while accounting for [redacted] (b) (4) of the [redacted] (b) (4). The revised assay will be submitted together with the validation report.

The timetable you submitted on November 14, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission as a prior approval supplement: September 2012

Submit clinical protocols to your IND 000290 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP, see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Erik S. Laughner, M.S., RAC (US), Senior Regulatory Health Project Manager, at (301) 796-1393.

Sincerely,

/Richard Pazdur/
Richard Pazdur, M.D.
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling