DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125277/0

BLA APPROVAL
December 1, 2009

Dyax Corporation
300 Technology Square
Cambridge, MA 02139

Attention: Nicole D'Auteuil
Senior Director, Regulatory Affairs

Dear Ms. D'Auteuil:

Please refer to your biologics license application (BLA), dated September 23, 2008, received September 23, 2008, submitted under section 351 of the Public Health Service Act (PHSA) for Kalbitor (ecallantide) injection.

We acknowledge receipt of your submissions dated December 31, 2007, March 27, September 23, October 10 and 30, November 13, 18, and 26, and December 9, 11, 15, 19 (2), 23, 24, and 31, 2008, and January 5, 9, 13, 16, 21, 23, 27, 28, and 29, February 11, 12, 13, 20, and 27, March 9, May 31, June 10 and 29, July 21, August 12 and 31, September 29, October 26 (3) and 30 (2), November 9, 16, 17, 18, 19, 23 (2), 24, 25, and 27, and December 1, 2009.

The May 31, 2009, submission constituted a complete response to our March 25, 2009, action letter.

We have completed our review of your application and are issuing Department of Health and Human Services U.S. License No. 1789 to Dyax Corporation, Cambridge, Massachusetts, under the provisions of section 351(a) of the PHSA controlling the manufacture and sale of biological products. The license authorizes you to introduce into, or deliver for introduction into, interstate commerce those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Kalbitor (ecallantide) injection. Kalbitor (ecallantide) injection is indicated for the treatment of acute attacks of hereditary angioedema in patients 16 years of age and older.

Under this license, you are approved to manufacture ecallantide drug substance at (b) (4) The final formulated product will be manufactured, filled, labeled, and packaged at (b) (4) You may label your product with the proprietary name Kalbitor and market it as a sterile liquid in single-dose, 2-mL glass vials (1-mL fill), 10 mg/mL for subcutaneous injection.

You currently are not required to submit samples of future lots of Kalbitor (ecallantide) injection 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 to release of each lot.

You must submit information to your biologics license application for our review and written approval under 21 CFR 601.12 for any changes in the manufacturing, testing, packaging, or labeling of Kalbitor (ecallantide) injection, or in the manufacturing facilities.

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

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) 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 (section 505(o)(3)(A)).

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 assess a known serious risk of hypersensitivity reactions and immunogenicity, a theoretical risk of disordered coagulation, and an unexpected, serious risk of malignancy with use of Kalbitor (ecallantide) injection.

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

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

1. A long-term, observational safety study with Kalbitor (ecallantide) in patients with hereditary angioedema to evaluate hypersensitivity, immunogenicity, and coagulation disorders. The study should include the following objectives: 1) identify predictive risk factors and develop effective screening tools to mitigate the risk of hypersensitivity and anaphylaxis; 2) correlate antibody levels with adverse events and lack of efficacy; and 3) evaluate the risk of hypercoagulability and hypocoagulability.

The timetable you submitted on November 19, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission:	December 2009
Study Completion Date:	February 2014
Final Report Submission:	August 2014

2. Establish the sensitivity and cutpoint for the anti-ecallantide neutralizing antibody assay, using immunoaffinity-purified ecallantide-specific human IgG.

   The timetable you submitted on November 19, 2009, states that you will conduct this study according to the following timetable:

   Final Report Submission: March 2010

3. Evaluate for cross-reactivity of anti-ecallantide antibodies with TFPI, perform studies to determine if human anti-ecallantide antibodies bind TFPI, and perform suitability studies and epitope mapping of the human anti-ecallantide antibody response if binding is observed.

   The timetable you submitted on November 19, 2009, states that you will conduct this study according to the following timetable:

   Final Report Submission: August 2010

4. Develop and validate anti-ecallantide and anti-*P. pastoris*-specific human IgE detection assays using a sensitive platform such as ECL. Such assays should be free from interference by anti-ecallantide IgG antibodies.

   The timetable you submitted on November 19, 2009, states that you will conduct this study according to the following timetable:

Method Development Reports Submission:	April 2010
Final Report Submission:	September 2010

5. A study in rats to evaluate the carcinogenic potential of Kalbitor (ecallantide). The six-month subcutaneous toxicology study with rats could serve as the basis of dose selection.

   The timetable you submitted on November 19, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission:	June 2010
Study Completion Date:	September 2012
Final Report Submission:	September 2013

Submit the protocols to your IND, with a cross-reference letter to this BLA 125277. Submit all final reports to your BLA 125277. Prominently identify submissions 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 SUBJECT TO REPORTING REQUIREMENTS OF SECTION 506B

We acknowledge your written commitments as described in your letter of November 24, 2009, as outlined below:

6. The submission, as a pre-approval supplement, of an updated stability protocol for drug product that will add an accelerated or stress stability condition as part of the annual stability program. The data accumulated from this protocol will be submitted to the BLA on an annual basis.

   Final Protocol Submission: January 2010

7. To evaluate the minimum fill volume required to provide appropriate dosage withdrawal and whether an adjustment to the fill volume for the drug product is necessary to reduce the likelihood that a patient will be overdosed with any excess drug product. The final study report including identification of a new fill volume, if found to be necessary, will be provided. Should the fill volume need to be changed, this report will include a proposed execution plan.

   Final Report Submission: April 2010

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

Your proposed REMS, submitted on December 1, 2009, and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include but is not limited to the following:

a. A summary of all reported serious hypersensitivity reactions with analysis of adverse event reporting by prescriber type.

b. Specification of measures that would be taken to increase awareness if surveys of health care providers indicate that provider awareness is not adequate.

c. An evaluation of health care providers' understanding and patients' understanding of the serious risks of Kalbitor (ecallantide) injection.

d. Based on the information submitted, an assessment and conclusion of whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any post-approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B, and 21 CFR 601.70, and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.
Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

BLA 125277
REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 125277
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR BLA 125277
REMS ASSESSMENT
PROPOSED REMS MODIFICATION *(if included)*

If you do not submit electronically, please send five copies of REMS-related submissions.

We request that the labeling approved today be available on your website within 10 days of product launch.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). In addition, you should submit all reports of serious anaphylactic or hypersensitivity events within 15 days of receipt as 15-day expedited reports. 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 4203
Silver Spring, MD 20992-0002

CONTENT OF LABELING

Within 14 days of the date of this letter, submit content of labeling (21 CFR 601.14(b)) in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm that is identical in content to the enclosed labeling (text for the package insert and Medication Guide submitted November 27, 2009). The content of labeling should be submitted by updating your application by referencing the SPL file submitted to the drug establishment registration and drug listing system. To do this, place a link in your application submission that directs FDA to your SPL file. For administrative purposes, please designate this submission "**Product Correspondence – Final SPL for approved BLA STN 125277**." In addition, within 14 days of the date of this letter, amend any pending supplements for this BLA with content of labeling in SPL format to include the changes approved in this supplement. For additional information on submitting labeling to drug establishment registration and drug listing and to applications, see the FDA guidances at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072339.pdf and http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

CARTON AND CONTAINER LABELS

Submit final printed carton and container labels that are identical to the labels submitted November 23, 2009, 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 (October 2005).* 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 125277**." Approval of this submission by FDA is not required before the labeling is used.

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

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
Division of Drug Marketing, Advertising, and Communications
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 Division of Drug Marketing, Advertising, and Communications, 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.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this BLA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

POST-ACTION FEEDBACK MEETING

New molecular entities and important 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 the drug development and marketing application review process. 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, contact the Division of Pulmonary and Allergy Products.

If you have any questions, contact the Senior Regulatory Health Project Manager, Colette Jackson, at (301) 796-1230.

Sincerely,

/Curtis J. Rosebraugh, M.D., M.P.H./
Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
REMS documents
Package Insert
Medication Guide
Carton and Container Labels