CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125277

OTHER ACTION LETTER(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Our STN: BL 125277/0

COMPLETE RESPONSE

Dyax Corporation
300 Technology Square
Cambridge, MA 02139

MAR 25 2009

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 for Kalbitor (ecallantide) injection.

We acknowledge receipt of your submissions dated December 31, 2007, March 27, 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, and February 11, 12, 13, 20, and 27, and March 9, 2009.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

CLINICAL

1. The results of the submitted clinical studies do not support the efficacy and safety of Kalbitor (ecallantide) at a dose of 30 mg SC for the treatment of acute attacks of hereditary angioedema (HAE) in patients 10 years of age and older. Particularly, the number of patients below 18 years of age exposed to Kalbitor (ecallantide) is limited and not adequate to assess efficacy or safety in this age group. To support efficacy and safety of Kalbitor (ecallantide) for treatment of acute attacks of HAE in patients 10 years of age and older, provide the following: Efficacy and safety data from controlled clinical studies or open label clinical studies in a reasonable number of patients below 18 years of age and covering each year age group. Also provide validation of the ecallantide bio-analytical assay, and comparative ecallantide exposure data in adults and pediatric patients to support the recommended pediatric dose.

2. Requirement for proposed Risk Evaluation and Mitigation Strategy (REMS). For the reasons described below, a REMS will be required as part of your approval.

PRODUCT QUALITY

3. Sufficient information regarding depyrogenation of the 2 mL glass vials has not been provided.

   a. Describe the load configuration that includes the 2 mL glass vial. The January 16, 2009, amendment does not identify this load.

   b. Provide the minimum lethality values for the loads validated and for the load that includes the 2 mL glass vial.

   c. Describe the minimum load configurations and rationale.

4. Validation studies for stopper sterilization were performed using biological indicator spore strips and ampoules. We recommend that studies be performed using a biological indicator spore suspension directly inoculated onto the stoppers due to the variation in D-values that may result from using indicator strips and ampoules. Alternatively, you may provide data to demonstrate that the bioburden of incoming stoppers has resistance that does not exceed that of the biological indicator used in the validation studies.

5. With regard to assay sensitivity, the sensitivity of the dye ingress container-closure integrity test has not been provided. Provide the smallest volume of dye that can be detected under the provided test conditions.

6. As provided for by 21 CFR 610.9, submit a formal request to waive the requirement for a bulk sterility test.

7. Regarding cell bank characterization:

   a. We acknowledge that assessment of the cell banking system for the presence of (b) (4) has been conducted and that no (b) (4) was detected in the working cell bank. However, information describing the assay's Limit of Detection (LOD), a critical measure indicating that the assay provides meaningful results, has not been submitted. Provide information regarding the procedures used and the results obtained for determination of the LOD for the (b) (4) assay.

   b. You have included a protocol to assess qualification of a new working cell bank which, if approved, would allow you to submit results of the qualification study in the subsequent annual report. Although you have characterized the current working cell bank to ensure consistent production of the intended product, the proposed protocol is deficient in ensuring the consistency of critical product quality attributes. Thus, while consistency of the coding sequence of the expression construct is a critical parameter, it is not sufficient to ensure that the intended product is consistently produced since some product attributes (e.g.

glycosylation) cannot be predicted from sequence alone. Revise your protocol to include a full characterization of the intended product and results to be achieved.

c. Studies pertaining to the examination of extractable and leachable substances associated with the drug substance (DS) and drug product (DP) container/closure systems have not been performed using the relevant DS and DP vehicles. While extractable data generated by the vendor is useful and the risk due to the potential toxicity of these leachables appears minimal, the risks associated with potential for enhanced immunogenicity due to an adjuvant effect have not been addressed. You will need to evaluate the amounts and types of leachables that accumulate over time under the recommended storage conditions, using robust analytical methods. Submit the results of these evaluations.

8. Regarding the release and stability specifications:

a. Your potency assay used for release and stability testing of drug substance and drug product appears to be inadequate. Under the conditions of the proposed assay, Ki_{app} is much less then the amount of enzyme (E) and therefore, all inhibitor will be bound to enzyme irrespective of significant changes in the affinity of ecallantide to Kallikrein. Thus, a given lot of ecallantide would not be out of specification until the Ki_{app} is approximately (b) (4) than the expected value of (b) (4) We believe that determination of Ki_{app} as a release assay will provide a better measure of product potency then the currently proposed test, if the precision of the Ki_{app} determination is improved. Furthermore, the Ki_{app} assay should be designed so that inhibitor concentrations are tested in a range of concentrations relative to enzyme active site concentrations (less than, equal to, and greater than) with an emphasis on data points in the region where [I] approximates [E]. Revise the specifications to include a measurement of Ki_{app}.

b. The following comments pertain to your SDS-PAGE analysis.

(b) (4)

(b) (4)

c. The following comments pertain to your specifications for the RP-HPLC assay.

(1) You have proposed to group oxidized variants together with glycosylated species in your release and stability specifications. However, because each variant is associated with different risks to patient safety, we believe each of these variants should have individual acceptance criteria. Revise the acceptance criteria to include separate limits for oxidized and glycosylated species.

(2) Currently, your specification for main peak plus product related substance is (b) (4)%. This allows for up to (b)% of unknown total impurities. However, actual results show that product related substances compose (% of the total material with no other substances observed. Revise b your acceptance criteria to better reflect actual manufacturing history.)

(3) While you have specified that no single impurity will be (b)%, this does not take into account the risk associated with a specific impurity. Revise your specifications to include action limits that require an assessment of impact to product quality as it may relate to safety and efficacy, for any new impurity that is observed in the RP-HPLC assay.

(4) The acceptance criteria for (b) (4)) for release and stability are (b) and (b)% respectively. However, you have not adequately justified these levels. While we understand this is a product related substance (i.e., has biological activity), (b) (4) levels may also influence immunogenicity of the product. Submit data that support these acceptance criteria with your justification.

d. Express the acceptance criterion for results from the (b) (4) assay using 2 significant figures (b) (4)

e. (b) (4)

f. (b) (4)

(b) (4)

g. (b) (4)

9. Given that you ship drug substance to a contract manufacturer for fill/finish, it is important that an identity test be performed at the contract manufacturer to ensure the correct identity of the product to be manufactured. Describe the identity testing performed for receipt at the contract manufacturer for fill/finish.

10. The acceptance criteria listed in your reference standard qualification protocol are not sufficiently stringent to control for potential drift in the characteristics of the reference standard. For example, the acceptance criterion for bioactivity is (b)% to (b)% and thus allows for a standard having an actual activity value of (b)% to represent (b)% activity for a test sample, thereby introducing a (b)% change in the true potency of the product. Tighten each acceptance criterion to minimize drift in product characteristics. Include objective criteria for assessing what "comparable to reference standard" means.

11. You established (b) (4) based on manufacturing experience and a statistical analysis using (b)% tolerance intervals. This approach allows for action limits for step yields that are significantly (b) (4) than current manufacturing experience indicates has no impact on product quality. Tighten the range to better reflect your actual manufacturing experience and your understanding of how yield can impact product quality.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a REMS if the FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

The data submitted in your BLA show that Kalbitor (ecallantide) is immunogenic and that there is a risk of anaphylaxis following treatment. Anaphylaxis was noted as a safety signal in the clinical data submitted to support the efficacy and safety of Kalbitor (ecallantide). Using

diagnostic criteria for anaphylaxis as outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis[1], 9 potential cases of anaphylaxis were identified out of 243 HAE patients treated with Kalbitor (ecallantide) (an anaphylaxis rate of 3.7%). Most of these reactions occurred following repeated dosing with Kalbitor (ecallantide).

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Kalbitor (ecallantide) to ensure that the benefits of the drug outweigh the risks of anaphylaxis. The REMS, once approved, will create enforceable obligations. You submitted a proposed REMS dated February 27, 2009, which was not reviewed for this action. Before this BLA may be approved, you must submit an amended proposed REMS with the following elements, as described below.

Your proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Kalbitor (ecallantide) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Kalbitor (ecallantide). FDA has determined that Kalbitor (ecallantide) is a product that has a serious risk (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use, or continue to use Kalbitor (ecallantide). FDA has also determined that Kalbitor (ecallantide) is a product for which patient labeling could help prevent serious adverse events. Under 21 CFR Part 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Kalbitor (ecallantide).

Communication Plan: We have determined that a communication plan targeted to healthcare providers who are likely to prescribe Kalbitor (ecallantide) will support implementation of the elements of your REMS. The communication plan must provide for the dissemination of information about the risk of anaphylaxis associated with Kalbitor (ecallantide). See 505-1(e)(3).

Elements to Assure Safe Use: We have determined that Kalbitor (ecallantide) can be approved only if elements to assure safe use are required as part of the REMS to mitigate a specific serious risk listed in the labeling, anaphylaxis.

Your REMS must include at a minimum, the following elements to assure safe use:

- A requirement that healthcare providers who prescribe Kalbitor (ecallantide) have particular training or experience or are specially certified under 505-1(f)(3)(A).
- A requirement that Kalbitor (ecallantide) is only dispensed by pharmacies, practitioners, or healthcare settings that are specially certified under 505-1(f)(3)(B).

[1] Sampson HA et al. J Allergy Clin Immunol 2006; 117:391-7.

- A requirement that Kalbitor (ecallantide) is dispensed or administered to patients with documentation of safe-use conditions under 505-1(f)(3)(D).

- A requirement that each patient using Kalbitor (ecallantide) be subject to certain monitoring under 505-1(f)(3)(E).

- A requirement that patients who receive Kalbitor (ecallantide) are enrolled in a registry under 505-1(f)(3)(F).

Implementation System: The REMS must include an implementation system to monitor and evaluate the implementation of the elements to assure safe use required under 505-1(f)(3)(B) and (D) by parties in the health care system responsible for their implementation. The implementation system must also include a plan to address any findings of inadequate implementation of these elements to assure safe use.

Timetable for Assessments: The proposed REMS must include a timetable for submission of assessments of the REMS that shall be no less frequent than every 6 months for the first 2 years and annually thereafter after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Each assessment must assess the extent to which the elements of your REMS are meeting the goals of your REMS and whether the goals or elements should be modified.

We suggest that your proposed REMS submission include two parts: a "Proposed REMS" and a "REMS Supporting Document." Attached is a template for the Proposed REMS that you should complete with concise, specific information (see Appendix A). Include information in the template that is specific to your proposed REMS for Kalbitor (ecallantide). Additionally, all relevant proposed REMS materials including educational and communication materials should be appended to the proposed REMS. Once FDA finds the content acceptable and if the drug is approved, we will include these documents as an attachment to the approval letter that includes the REMS.

The REMS Supporting Document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

Information needed for the assessments should include but may not be limited to:

- Patients' and healthcare providers' understanding of the serious risks of Kalbitor (ecallantide).

- A report on the status of the training and certification of prescribers, including failures to adhere to the training.
- A report on the status of certification of pharmacies, practitioners, or healthcare settings that dispense Kalbitor (ecallantide), including failures to obtain certification.
- A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address non-compliance.
- A report on the status of the patient registry, including failures to enroll patients into the registry.

If you do not submit electronically, please send 5 copies of your proposed REMS as an amendment to your application. Prominently identify all subsequent proposed REMS submissions with the following wording in bold capital letters at the top of the first page of the submission.

BLA 125277 PROPOSED REMS-AMENDMENT

LABELING

We reserve comment on the proposed labeling and labels until the application is otherwise adequate. If you revise labeling, your response must include updated 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. The carton and vial labels will need to be revised to state that the product is (b) (4) Also, note that the following bolded statement or appropriate alternative must be included on the carton and vial labels per 21 CFR 208.24(d): **"ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide".**

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the initial submission.
   - Present tabulations of the new safety data combined with the initial data.
   - Include tables that compare frequencies of adverse events in the initial data with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the initial data.

6. Provide updated exposure information for the clinical trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of any currently approved foreign labeling not previously submitted.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize 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), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

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 the known serious risk of anaphylaxis and to identify unexpected serious risks of immunogenicity, coagulation effects, and carcinogenicity in patients taking Kalbitor (ecallantide).

Therefore, based on appropriate scientific data, FDA has determined that you will be required, pursuant to section 505(o)(3) of the FDCA, to conduct the following studies if your application is approved.

1. Conduct a study with Kalbitor (ecallantide) in patients with hereditary angioedema to evaluate anaphylaxis and type I hypersensitivity. The study should include objectives to identify predictive risk factors and develop effective screening tools to mitigate the risk of hypersensitivity and anaphylaxis.

2. Conduct a study with Kalbitor (ecallantide) in patients with hereditary angioedema to evaluate immunogenicity. The study should include objectives to correlate antibody levels with adverse events and lack of efficacy.

3. Conduct a study with Kalbitor (ecallantide) in patients with hereditary angioedema to evaluate the effects on coagulation parameters.

4. Conduct a study in rats to evaluate the carcinogenic potential of Kalbitor (ecallantide). We recommend that you submit a dose escalation proposal for the carcinogenicity study with rats for our review and concurrence prior to initiation of the study. The 6-month subcutaneous toxicology study with rats could serve as the basis of dose selection.

OTHER

While not approvability issues, we have the following comments and requests for additional information.

A. Three different assays were used to measure the ecallantide concentration. However, some key information was missing in these assay reports. The agency sent an information request letter requesting the missing information on December 4, 2008. You replied on January 29, 2009. However, some information was still missing. In the teleconference on February 11, 2009, we requested you re-submit the reports with LLOQ, QC and calibration curve information for all the in-study bio-analytical reports from (b) (4) (b) (4) Therefore, you should resubmit the reports with required information. If any bio-analytic assay is considered invalid, then the data from this assay should not be used in the population pharmacokinetics analysis. We may request you to repeat the population pharmacokinetics analysis by using the data only from the validated assays.

B. The following comments pertain to the ELISA for measuring DX-88 in plasma (SOP QC-52-15).

1. Assay specificity:

(b) (4)

(b) (4)

6 pp withheld immediately after this page as (b)(4) CCI/TS.

(b) (4)

G. The following comments pertain to the validation of anti-*P. pastoris* IgE Antibody ELISA (TNJR07-085 & ITR 335-1106).

1. (b) (4)

2. (b) (4)

(a) (b) (4)

(b) (b) (4)

(c)

3. (b) (4)

Within one year after the date of this letter, you are required to resubmit or withdraw the application. If you do not take any of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). A resubmission must fully address

all the deficiencies listed, and will start a new review cycle. A partial response may not be reviewed and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application can be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry on *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (http://www.fda.gov/cder/guidance/2125fnl.htm).

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

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

Sincerely,

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

Enclosures: REMS Appendices A and B

Appendix A: REMS Template

If you are not proposing to include one of the listed elements, include a statement that the element is not necessary.

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name
Address
Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide or PPI

If a Medication Guide is included in the proposed REMS, include the following:

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

If a Communication Plan is included in the proposed REMS, include the following:

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Include a description of the intended audience, including the types and specialties of healthcare providers to which the materials will be directed. Include a schedule for when and how materials will be distributed. Append the printed material and web shots to the REMS Document.

C. Elements To Assure Safe Use

If one or more Elements to Ensure Safe Use are included in the proposed REMS, include the following:

List elements to assure safe use of Section 505-1(f)(3)(A-F) included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);

D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;

E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or

F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

D. Implementation System

If an Implementation System is included in the proposed REMS, include the following:

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B),(C), and (D), listed above .

E. Timetable for Submission of Assessments

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Appendix B: Supporting Document

This REMS Supporting Document should include the following listed sections 1 through 5, as well as a table of contents. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 3 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

TABLE OF CONTENTS

1. Background
2. Goals
3. Supporting Information on Proposed REMS Elements
    a. Additional Potential Elements
        i. Medication Guide
        ii. Patient Package Insert
        iii. Communication Plan
    b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
    c. Implementation System
    d. Timetable for Assessment of the REMS
4. Information Needed for Assessments
5. Other Relevant Information