CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125277

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Exclusivity Request

In accordance with Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and Title 21 CFR 314.108(b)(2), Dyax Corp. claims exclusivity for KALBITOR™ (ecallantide). The active moiety in KALBITOR™ (ecallantide) is a new chemical entity, and had not been previously used for marketing under section 505(b). Under the Orphan Drug Act of January 4, 1983, and its amendments in 1984, 1985, and 1988, the developer of an orphan product is guaranteed seven years of market exclusivity following approval of the product by the FDA. This product that is the subject of this Biologics License Application was granted Orphan Drug Designation on 04 February 2003 (designation 02-1608). Therefore, Dyax requests and claims 7 years of market exclusivity following approval of this Biologics License Application.

Date: 17 Sept 2008

Nicole D'Auteuil
Senior Director, Regulatory Affairs
Dyax Corp.

Request for Pediatric Waiver

KALBITOR™ (ecallantide), the subject of this Biologics License Application, was granted Orphan Drug Designation on 04 February 2003 (designation 02-1608). Based on the orphan status of ecallantide in the treatment of hereditary angioedema (HAE), this application qualifies for a pediatric exemption as described in 21 CFR 314.55(d).

Date: 17 Sept 2008

Nicole D'Auteuil
Senior Director, Regulatory Affairs
Dyax Corp.

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

)A/BLA#: 125277 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: Pulmonary and Allergy Products PDUFA Goal Date: December 1, 2009 Stamp Date: 6/1/2009

Proprietary Name: Kalbitor

Established/Generic Name: ecallantide

Dosage Form: Injection

Applicant/Sponsor: Dyax

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: Hereditary Angioedema

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)

ason(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):

te: 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∆
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ 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.

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
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	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, 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?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

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):

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

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	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 diatric 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?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

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

e 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

OCT 20 2009

(Revised: 6/2008)

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

Debarment Certification

Dyax Corp., 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.

Date: 17 Sept 2008

Nicole D'Auteuil
Senior Director, Regulatory Affairs
Dyax Corp.

NDA/BLA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

Application Information		
NDA # BLA# 125277	NDA Supplement #:S- BLA STN # 0	Efficacy Supplement Type SE-
Proprietary Name: Kalbitor Established/Proper Name: ecallantide Dosage Form: Injection Strengths: 10mg/mL		
Applicant: Dyax Agent for Applicant (if applicable):		
Date of Application: September 23, 2008 Date of Receipt: September 23, 2008 Date clock started after UN: N/A		
PDUFA Goal Date: March 23, 2009	Action Goal Date (if different):	
Filing Date: November 21, 2008 Date of Filing Meeting: October 30, 2008		
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed Indication(s): Treatment of Hereditary Angioedema		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***Refer to Appendix A for further information.***	☐ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.***	☐ Standard ☒ Priority ☐ Tropical disease Priority review voucher submitted
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☒ Fast Track ☒ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ 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): 10,426	
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☐ YES ☒ NO
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.***	☒ YES ☐ NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	☒ YES ☐ NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ora/compliance_ref/aiplist.html*** **If yes**, explain: **If yes**, has OC/DMPQ been notified of the submission? **Comments:**	☐ YES ☒ NO ☐ YES ☐ NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	☐ YES ☒ NO
User Fee Status **Comments:**	☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).*	
Exclusivity	
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm*** **If yes**, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?	☐ YES ☒ NO ☐ YES ☐ NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) **Comments:**	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)***- *Sponsor has requested 7 years of exclusivity under the Orphan Drug Act.* ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.* **Comments:**	☐ YES # years requested: ☐ NO
If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***): 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)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***	☐ Not applicable ☐ YES ☐ NO
505(b)(2) (NDA/NDA Efficacy Supplements Only)	
	☐ **Not applicable**
1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☐ NO
2. 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)).	☐ YES ☐ NO
3. 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))? ***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).*	☐ YES ☐ NO

4. 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:	☐ YES ☐ NO

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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.

Format and Content

Do not check mixed submission if the only electronic component is the content of labeling (COL). **Comments:**	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	
If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)? *Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.* **Comments:**	☒ YES ☐ NO
If electronic submission, does it follow the eCTD guidance? (*http://www.fda.gov/cder/guidance/7087rev.pdf*) **If not,** explain (e.g., waiver granted):	☒ YES ☐ NO

Form 356h: Is a signed form 356h included? ***If foreign applicant, both the applicant and the U.S. agent must sign the form.*** Are all establishments and their registration numbers listed on the form? **Comments**: Establishments are listed but are not yet registered.	☒ YES ☐ NO ☐ YES ☒ NO
Index: Does the submission contain an accurate comprehensive index? **Comments**:	☒ YES ☐ NO
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain:	☒ YES ☐ NO
Controlled substance/Product with abuse potential: Abuse Liability Assessment, including a proposal for scheduling, submitted? Consult sent to the Controlled Substance Staff? **Comments**:	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
BLAs/BLA efficacy supplements only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐ YES ☐ NO
Patent Information (NDAs/NDA efficacy supplements only)	
Patent information submitted on form FDA 3542a? **Comments**:	☐ YES ☐ NO
Debarment Certification	
Correctly worded Debarment Certification with authorized signature? ***If foreign applicant, both the applicant and the U.S. Agent must***	☒ YES ☐ NO

sign the certification. ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) 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..."* **Comments:**	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
Field Copy Certification: that it is a true copy of the CMC technical section (***applies to paper submissions only***) ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐ Not Applicable (*electronic submission or no CMC technical section*) ☐ YES ☐ NO
Financial Disclosure	
Financial Disclosure forms included with authorized signature? ***Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.* **Comments:**	☒ YES ☐ NO
Pediatrics	
PREA ***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.* Are the required pediatric assessment studies or a full waiver of pediatric studies included? Orphan Drug Designation **If no,** is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included? • ***If no, request in 74-day letter.*** • **If yes,** 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)	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO

Comments:	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).*** **Comments:**	☐ YES ☐ NO
Prescription Labeling	
Check all types of labeling submitted. **Comments:**	☐ **Not applicable** ☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☒ Instructions for Use ☐ MedGuide ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)
Is electronic Content of Labeling submitted in SPL format? ***If no, request in 74-day letter.*** **Comments:**	☒ YES ☐ NO
Package insert (PI) submitted in PLR format? **If no**, was a waiver or deferral requested before the application was received or in the submission? **If before**, what is the status of the request? ***If no, request in 74-day letter.*** **Comments:**	☒ YES ☐ NO ☐ YES ☐ NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **Comments:**	☒ YES ☐ NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (*send WORD version if available*) **Comments:**	☒ Not Applicable ☐ YES ☐ NO
REMS consulted to OSE/DRISK? **Comments:**	☒ Not Applicable ☐ YES ☐ NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP? **Comments:**	☐ Not Applicable ☒ YES ☐ NO

OTC Labeling	
Check all types of labeling submitted. **Comments:**	☐ **Not Applicable** ☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)
Is electronic content of labeling submitted? ***If no, request in 74-day letter.*** **Comments:**	☐ YES ☐ NO
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.*** **Comments:**	☐ YES ☐ NO
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.*** **Comments:**	☐ YES ☐ NO
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP? **Comments:**	☐ YES ☐ NO
Meeting Minutes/SPA Agreements	
End-of Phase 2 meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments:**	☒ YES Date(s): August 29, 2006 CMC EOP2 December 13, 2006 ☐ NO
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments:**	☒ YES Date(s): October 30, 2007 ☐ NO
Any Special Protocol Assessment (SPA) agreements? ***If yes, distribute letter and/or relevant minutes before filing meeting.*** **Comments:**	☒ YES Date(s): October 23, 2007 ☐ NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 30, 2008

NDA/BLA #: 125277

PROPRIETARY/ESTABLISHED NAMES: Kalbitor (ecallantide) Injection

APPLICANT: Dyax

BACKGROUND: New molecular entity for the treatment of hereditary angioedema
(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting (Y or N)
Regulatory Project Management	RPM:	Colette Jackson	Y
	CPMS/TL:	Sandy Barnes	N
Cross-Discipline Team Leader (CDTL)	Sally Seymour		Y
Clinical	Reviewer:	Susan Limb	Y
	TL:	Sally Seymour	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
OSE	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Yun Xu	Y
	TL:	Wei Qiu	Y
Biostatistics	Reviewer:	Dongmei Liu	Y
	TL:	Qian Li	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Jean Wu	Y
	TL:	Luqi Pei, Acting	Y
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Kathy Lee	Y
	TL:	Emily Schacter	Y
Facility (*for BLAs/BLA supplements*)	Reviewer:	Anastasia Lolas	N
	TL:	Patricia Hughes	Y
Microbiology, sterility (*for NDAs/NDA efficacy supplements*)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers			

OTHER ATTENDEES:

505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
Per reviewers, are all parts in English or English translation? **If no,** explain:	☒ YES ☐ NO

Electronic Submission comments **List comments:**	☐ Not Applicable
CLINICAL **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments:** ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***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***	☒ YES Date if known: February 4, 2009 ☐ NO ☐ To be determined Reason:
• 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? **Comments:**	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments:**	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Categorical exclusion for environmental assessment (EA) requested? **If no,** was a complete EA submitted? **If EA submitted,** consulted to EA officer (OPS)? **Comments:**	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
• Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments:**	☐ Not Applicable ☒ YES ☐ NO ☐ Not Applicable ☒ YES ☐ NO
• Sterile product? **If yes,** was Microbiology Team consulted for validation of sterilization? **(NDAs/NDA supplements only)**	☒ YES ☐ NO ☐ YES ☐ NO

FACILITY (BLAs only)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE
Comments:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Curtis Rosebraugh, Office Director, ODE II

GRMP Timeline Milestones:

Filing Meeting: October 30, 2008
Filing Reviews Due: November 14, 2008
60th Day Letter Due: November 21, 2008 (actual is Saturday, November 22nd))
Mid-Cycle Meeting: December 16, 2008
AC Practice#1: January 14, 2009
Labeling Meeting/AC Practice #2: January 21, 2009
AC Practice #3: January 28, 2009
AC Meeting: February 4, 2009
Wrap-Up: February 9, 2009
Labeling Tcon with Applicant: February 11, 2009
Primary Reviews/Draft CDTL Memo Due: February 16, 2009
Secondary Reviews/Draft CDTL Memo Due: February 23, 2009
CDTL Memo Due: March 2, 2009

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): ☐ Standard Review ☒ Priority Review

ACTIONS ITEMS

☒	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.

☐	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.
☒	If BLA or priority review NDA, send 60-day letter.
☐	Send review issues/no review issues by day 74
☐	Other

COLETTE JACKSON, RPM 11/12/08

SANDY BARNES, CPMS 11/12/08

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.

BLA/NDA/PMA
Review Committee Assignment Memorandum

- ■ Initial Assignment
- ■ Change

STN: 125277/0

Applicant: Dyax Corporation

Product: Kalbitor (ecallantide)

Addition of committee members

Name	Reviewer Type*	Job Type	Assigned by	Date
Colette Jackson	Reg. Project Manager	Admin/Regulatory	Sandy Barnes	9/23/2008
	Reviewer	Admin/Regulatory		
Kathy Lee	Reviewer	Product*	Amy Rosenberg	9/26/2008
Anastasia Lolas	Reviewer	Product*- Facilities	Patricia Hughes	9/30/2008
Jack Ragheb	Reviewer	Product-Immunogenicity	Amy Rosemberg	9/26/2008
Sally Seymour	CDTL	Clinical	Badrul Chowdhury	9/23/2008
Susan Limb	Reviewer	Clinical	Lydia Gilbert-Mcclain	9/28/2008
Yun Xu	Reviewer	Clinical Pharmacology	Wei Qiu	9/26/2008
Jean Wu	Reviewer	Pharm/Tox	Luqi Pei	9/30/2008
Dongmei Liu	Reviewer	Biostatistics	Qian Li	10/3/2008
	Reviewer	BiMo		
Tara Turner	Consultant Reviewer	Safety Evaluator	Denise Toyer	9/23/2008
	Reviewer	CMC, Facility*		
Kimberly Rains	Reviewer	Labeling	Amy Rosenberg	2/3/2009
Nancy Carothers	Reviewer	DRISK	Jodi Duckhorn	9/23/2008
Jessica Adams	Reviewer	DDMAC	Shefali Doshi	9/23/2008

*add inspector, if applicable

Deletion of Committee Member

Name	Reviewer Type*	Job Type	Changed by	Date

***reviewer types:** chairperson, consultant reviewer, regulatory coordinator, reviewer, and reg. project mgr (RPM)

Submitted by RPM:

COLETTE JACKSON — Name Printed

Signature

10/3/08 — Date

Memo entered in RMS by: Colette Jackson Date: 10/3/08 QC by: _____ Date: _____

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: November 27, 2009

To: Nicole D'Auteuil	**From:** Colette Jackson
Company: Dyax	Division of Pulmonary and Allergy Products
Fax number:	**Fax number:** 301-796-9718
Phone number:	**Phone number:** 301-796-1230
Subject: BLA 125277 FDA Package Insert and Medication Guide Comments	
Total no. of pages including cover:	

Comments:

Document to be mailed: YES xNO

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NOV 27 2009

BLA 125277
Kalbitor

Please refer to your May 31, 2009, biologics license application (BLA) resubmission for Kalbitor (ecallantide). We also refer to your submissions dated November 9, and 23, and 25, 2009. We have the following comments and labeling recommendations for the proposed Package Insert and Dear Health Care Provider Letter. These comments are not all-inclusive and we may have additional comments. Submit revised draft labeling incorporating the changes outlined in our enclosed labeling by noon November 30, 2009.

1. Insert a horizontal line separating the table of contents from the full prescribing information.

2. Due to SPL Release 4 validation, the Medication Guide can no longer be included as a subsection of Section 17. Attach the Medication Guide at the end of the package insert without numbering.

3. Update the Dear Health Care Provider letter to maintain consistency with the wording of the Boxed Warning in the package insert.

If there are any questions, please contact Ms. Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

/Colette Jackson/
Colette Jackson
Senior Regulatory Health Project Manager

Enclosure: Recommendations to the Package Insert and Medication Guide

Drafted: CCJ/ November 27, 2009
Initialed:

Jackson for Barnes/ November 27, 2009
Limb/November 27, 2009

Finalized: CCJ/ November 27, 2009

Filename: 125277 November 2009 SEALD Labeling Fax.doc

13 Page(s) of Draft Labeling have been Withheld in Full following this page as B4 (CCI/TS)

Dyax Corp.

300 Technology Square
Cambridge, MA 02139
phone (617) 225-2500
fax (617) 225-2501

Dyax

24 November 2009

BLA # 125277, Sequence 0054

Badrul Chowdhury, M.D., Ph.D.
Division of Pulmonary and Allergy Products
Center for Drug Evaluation and Research
Food and Drug Administration
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: KALBITOR® (ecallantide) Injection for Treatment of Hereditary Angioedema
BLA 125277; Sequence 0054
Amendment to Pending Application: Response to FDA Request- Post Marketing Commitments

Dear Dr. Chowdhury,

This amendment contains Dyax post-marketing commitments for CMC:

- To provide a stability protocol for annual accelerated or stress testing of the drug product
- To provide a report of an evaluation of the drug product fill volume

A brief synopsis is attached describing how we plan to address each area and the associated timetables. The synopsis for each study takes into account the FDA communication dated 17 November 2009 and the phone calls held on 17 and 24 November 2009.

This amendment is submitted in fully electronic (eCTD) format following ICH DTD 3.2 and FDA files specifications version 1.3 requirements. This submission was created and validated using a validated system. The application was virus scanned using Sophos Anti-Virus, version 7.6.13.

Please contact me at 617.250.5773 or via e-mail at ndauteuil@dyax.com or Aurelie Grienenberger at 617.250.5762 or via email at agrienenberger@dyax.com with any questions or requests regarding this submission.

Sincerely,

Nicole D'Auteuil
Senior Director, Regulatory Affairs
Phone: 617.250.5773; Facsimile: 617.225.2501

KALBITOR® (ecallantide) Post Marketing Commitments – Synopsis of commitments

Dyax commits to the following:

a) 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.

   Supplement Submission of Stability Protocol: January 2010

b) To evaluate the minimal 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 could be overdosed with any excess drug product. The final study report including identification of 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.

   Submission of Final Report: April 2010

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: November 24, 2009

To: Nicole D'Auteuil	**From:** Colette Jackson
Company: Dyax	Division of Pulmonary and Allergy Products
Fax number:	**Fax number:** 301-796-9718
Phone number:	**Phone number:** 301-796-1230

Subject: BLA 125277 FDA Package Insert and Medication Guide Comments

Total no. of pages including cover:

Comments:

Document to be mailed: YES xNO

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BLA 125277
Kalbitor

NOV 24 2009

Please refer to your May 31, 2009, biologics license application (BLA) resubmission for Kalbitor (ecallantide). We also refer to your submissions dated November 9, and 23, 2009. We have the following labeling recommendations for the proposed Package Insert and Medication Guide. These comments are not all-inclusive and we may have additional comments. Submit revised draft labeling incorporating the changes outlined in our enclosed labeling by COB November 25, 2009.

If there are any questions, please contact Ms. Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

/Colette Jackson/
Colette Jackson
Senior Regulatory Health Project Manager

Enclosure: Recommendations to the Package Insert and Medication Guide

16 pp withheld as draft labeling (b) (4)

Drafted: CCJ/ November 24, 2009
Initialed:

Barnes/ November 24, 2009
Limb/November 24, 2009

Finalized: CCJ/ November 24, 2009

Filename: 125277 November 2009 MG Labeling Fax.doc

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: November 20, 2009

To: Nicole D'Auteuil	**From:** Colette Jackson
Company: Dyax	Division of Pulmonary and Allergy Products
Fax number:	**Fax number:** 301-796-9718
Phone number:	**Phone number:** 301-796-1230

Subject: BLA 125277 FDA Carton and Container Labeling Comments

Total no. of pages including cover:

Comments:

Document to be mailed: YES xNO

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BLA 125277
Kalbitor

Please refer to your May 31, 2009, biologics license application (BLA) resubmission for Kalbitor (ecallantide). We also refer to your submission dated October 26, 2009. We have the following comments and labeling recommendations for the proposed carton and container labeling. These comments are not all-inclusive and we may have additional comments. Submit revised draft labeling incorporating the changes outlined in our comments by COB November 23, 2009.

1. The following comments pertain to the container labeling.

   a. Relocate the product strength so that it appears directly beneath the established name.

   b. To comply with 21 CFR 207.35 (b)(3)(i), ensure that the NDC number appears prominently in the top third of the principal display panel.

   c. If space permits, add the route of administration (e.g. for subcutaneous use only).

   (b) (4)

2. The following comments pertain to the proposed carton labeling.

   a. Increase the prominence of the product strength (10 mg/mL) and the net quantity statement (3 vials) by increasing the font size and weight.

   b. To comply with 21 CFR 207.35 (b)(3)(i), ensure that the NDC number appears prominently in the top third of the principal display panel.

   c. (b) (4)

If there are any questions, please contact Ms. Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

/Colette Jackson
Colette Jackson
Senior Regulatory Health Project Manager

Drafted: CCJ/ November 20, 2009
Initialed:

Jackson for Barnes/ November 20, 2009
Limb/November 20, 2009

Finalized: CCJ/ November 20, 2009

Filename: 125277 November 2009 DMEPA Labeling fax.doc

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: November 19, 2009

To: Nicole D'Auteuil	**From:** Colette Jackson
Company: Dyax	Division of Pulmonary and Allergy Products
Fax number:	**Fax number:** 301-796-9718
Phone number:	**Phone number:** 301-796-1230

Subject: BLA STN 125277 Response to October 26, and November 16, 2009, submissions

Total no. of pages including cover: 16

Comments:

Document to be mailed: **YES** **xNO**

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BLA STN 125277 November 19, 2009
Kalbitor

Please refer to your BLA resubmission dated June 1, 2009. We also refer to your October 26, and November 16, 2009, submission which provided your draft Risk Evaluation and Mitigation Strategy (REMS) for Kalbitor. We have the following comments and proposed revised REMS. These comments are not all-inclusive and we may have additional comments as your REMS submission(s) undergo further review. Please ensure that all communication materials accurately reflect the most recent language used in labeling. We ask that you respond to our comments and submit the revised proposed REMS with appended materials and the REMS Supporting Document by COB November 23, 2009, in order to facilitate our review. Please provide a track changes and clean version of all revised materials and documents.

1. Revise t (b) (4) s as follows:

a. (b) (4)

b. (b) (4)

(b) (4)

2 pp withheld immediately after this page as draft labeling, (b)(4).

(b) (4)

(b) (4)

4. Please submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS and appended materials be a single WORD document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single WORD document.

5. The survey instruments and methodology must be submitted to the FDA at least 90 days before you plan to conduct the evaluation. The submission should be coded "**REMS Correspondence**".

If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

/Colette Jackson/
Colette Jackson
Senior Regulatory Health Project Manager

Attachments: FDA Proposed REMS and REMS Support Documents

13 pp withheld immediately after this page as (b)(4) draft labeling

Drafted: November 19, 2009

Initialed: Barnes/ November 19, 2009
Seymour/ November 17, 2009

Finalized: CCJ/ November 19, 2009

Filename: 125277 November 2009 REMS DRISK fax.doc

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: November 17, 2009

To: Nicole D'Auteuil	**From:** Colette Jackson
Company: Dyax	Division of Pulmonary and Allergy Products
Fax number:	**Fax number:** 301-796-9718
Phone number:	**Phone number:** 301-796-1230

Subject: BLA STN 125277 Comments to Dyax

Total no. of pages including cover: 2

Comments:

Document to be mailed: YES xNO

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BLA STN 125277 NOV 17 2009
Kalbitor

Please refer to your BLA resubmission dated June 1, 2009. We also refer to your October 30, 2009, submission which outlined your Post Marketing Requirements for Kalbitor. We have the following comments. We ask that you respond to our comments by COB November 19, 2009, in order to facilitate our review.

1. (b) (4)

2. We ask you to consider the following as Post Marketing Commitments.

   a. To include an accelerated or stress stability condition as part of the annual stability program for the drug product.

      Submission of Final Report: (insert date)

   b. To evaluate the minimal fill volume required for appropriate dosage withdrawal and to adjust the final fill volume for the drug product to reduce the likelihood that a patient could be overdosed with the excess drug product. The final study report and new fill volume will be submitted in a supplement to the license.

      Submission of Final Report: (insert date)

If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Colette Jackson,
Senior Regulatory Health Project Manager

Drafted: November 16, 2009

Initialed: Barnes/ November 17, 2009
Ragheb/ November 17, 2009
Lee/ November 17, 2009

Finalized: CCJ/ November 17, 2009

Filename: 125277 November 2009 Immunogenicity and PMC fax.doc

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: November 13, 2009

To: Nicole D'Auteuil	**From:** Colette Jackson
Company: Dyax	Division of Pulmonary and Allergy Products
Fax number:	**Fax number:** 301-796-9718
Phone number:	**Phone number:** 301-796-1230
Subject: BLA STN 125277 Response to October 26, and 30, 2009, submissions	
Total no. of pages including cover: 12	

Comments:

Document to be mailed: YES xNO

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BLA STN 125277
Kalbitor

NOV 13 2009

Please refer to your BLA resubmission dated June 1, 2009. We also refer to your October 26, 2009, submission which provided your draft Risk Evaluation and Mitigation Strategy (REMS) and your October 30, 2009, submission which outlined your Post Marketing Requirements for Kalbitor. We have the following comments and proposed revised REMS. These comments are not all-inclusive and we may have additional comments. We ask that you respond to our comments by COB November 16, 2009, in order to facilitate our review.

1. The following comments pertain to the REMS.

   a. Revise REMS goal as follows:

      To inform healthcare providers about the risk of anaphylaxis associated with Kalbitor and the importance of distinguishing between a hypersensitivity reaction and hereditary angioedema (HAE) attack symptoms

      To educate patients about the serious risks associated with Kalbitor therapy

   b. Revise the Communication Plan as follows:

      (1) Please clarify that the contact database provided by (b) (4) (b) (4) will include all members of the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology. If the database does not, please include these membership lists as part of the dissemination plan.

      (2) Dyax will send the communication plan materials to targeted providers at the time of product launch and yearly for 2 years thereafter. Any new prescribers of Kalbitor should also be targeted in the communication plan. Revise the dissemination strategy to identify and reach new prescribers regardless of use or specialty for 2 years after product launch. These details should be included in the REMS and the REMS Supporting Document.

      (3) The follow up DHCP Letters should be updated if labeling changes for the hypersensitivity reaction risk are approved. Include this information in the Supporting Document.

      (4) We remind you that any component of a REMS proposal must be reviewed and approved by the FDA, including any post-approval modifications. Because of this requirement, we recommend creating a

direct link off the main website that includes REMS-specific materials. This link will direct users to a separate website that describes the REMS program and lists only approved REMS materials. The website should not be a means to promote Kalbitor or any other Sponsor product. Only this separate website or link will be considered a component of the Communication Plan.

c. Revise the timetable for assessment to 18 months, 3 years, and 7 years after approval.

d. The following comments pertain to the Information Needed for Assessment section of the REMS (REMS Assessment Plan).

   (1) Revise the Information Needed for Assessment (REMS Assessment Plan) in the Supporting Document to include the following:

      (i) A summary of all reported serious hypersensitivity reactions with analysis of adverse event reporting by prescriber type

      (ii) An evaluation of healthcare providers' understanding and patients' understanding of the serious risks of Kalbitor

      (iii) Specification of measures that would be taken to increase awareness if surveys of HCPs indicate that provider awareness is not adequate.

      (iv) A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24

      (v) A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

      (vi) 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.

   (2) We remind you to submit final methodology and instruments that were used to evaluate the effectiveness of the REMS with your required assessments.

e. Submit the revised Proposed REMS with appended materials and the REMS Supporting Document. Please provide a track changes and clean version of all revised materials and documents.

f. Please submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS and appended materials be a single WORD document. If certain documents such

as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single WORD document.

2. The following comment pertains to the Post Marketing Requirements.

We have revised your Post Marketing Requirements (PMR) outlined in your submission and have re-listed them below.

PMR#1: Conduct 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.

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

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

Submission of Final Report: March 2010

PMR#3: To evaluate for cross-reactivity of anti- ecallantide antibodies with TFPI, perform studies to determine if human anti- ecallantide antibodies bind TFPI and perform validation studies and epitope mapping of the human anti- ecallantide antibody response if binding is observed.

Submission of Final Report: March 2010

PMR#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.

Submit Method Development Reports for FDA Review: April 2010
Submission of Final Report: September 2010

PMR#5: Conduct a study in rats to evaluate the carcinogenic potential of Kalbitor (ecallantide). The 6-month subcutaneous toxicology study with rats could serve as the basis of dose selection.

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

If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Colette Jackson, Project Manager

Attachments: FDA Proposed REMS and Dear Health Care Provider Letter

Drafted: November 12, 2009

Initialed: Barnes/ November 12, 2009
Limb/ November 12, 2009
Seymour/ November 12, 2009

Finalized: CCJ/ November 13, 2009

Filename: 125277 November 2009 REMS and PMR fax.doc

6 pp withheld imemdiately following this page as (b)(4) draft labeling

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: November 5, 2009

To: Nicole D'Auteuil	**From:** Colette Jackson
Company: Dyax	Division of Pulmonary and Allergy Products
Fax number:	**Fax number:** 301-796-9718
Phone number:	**Phone number:** 301-796-1230

Subject: BLA 125277 FDA Proposed Labeling and Comments

Total no. of pages including cover:

Comments:

Document to be mailed: YES xNO

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NOV 5 2009

BLA 125277
Kalbitor

Please refer to your June 1, 2009, biologics license application (BLA) resubmission for Kalbitor (ecallantide). We also refer to your submission dated October 27, 2009. We have the following comments and labeling recommendations for the proposed Package Insert. The FDA-proposed insertions are underlined and deletions are in strike-out. These comments are not all-inclusive and we may have additional comments. Submit revised draft labeling incorporating the changes outlined in our enclosed labeling by COB November 9, 2009.

If there are any questions, please contact Ms. Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

/Colette Jackson/
Colette Jackson
Senior Regulatory Health Project Manager

Enclosure: Recommendations to the Package Insert and Medication Guide

Drafted: CCJ/ November 4, 2009
Initialed:

Barnes/ November 4, 2009
Limb/ November 5, 2009
Seymour/ November 5, 2009
Wu/ November 4, 2009
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15 pp withheld immediately following this page as (b)(4) Draft Labeling.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: October 28, 2009

To: Nicole D'Auteuil	**From:** Colette Jackson
Company: Dyax	Division of Pulmonary and Allergy Products
Fax number:	**Fax number:** 301-796-9718
Phone number:	**Phone number:** 301-796-1230

Subject: BLA STN 125277 Response to October 26, 2009, submission

Total no. of pages including cover: 4

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OCT 28 2009

BLA STN 125277
Kalbitor

Please refer to your BLA resubmission dated June 1, 2009. We also refer to your October 26, 2009, submission which posed questions regarding our October 16, 2009, communication. We have the following responses to your questions (in ***bold italics***) posed in the submission.

FDA Comment 3.a.(1):

For the anti-DX-88 neutralizing antibody assay, establish the clinically relevant LLOQ, ULOQ, LOD, and cutpoint for this assay using immunoaffinity purified DX-88-specific human IgG.

Dyax Questions:

1. ***Due to the semi-quantitative nature of neutralizing antibody assays in general and the lack of a specific, well characterized neutralizing antibody positive control for this assay, the LLOQ and ULOQ cannot be determined. However, the cutpoint and assay sensitivity, which will provide an estimate for the limit of detection (LOD) of the assay will be included as part of this requested work. Is this approach acceptable?***

FDA response:

Your approach is acceptable since this is not a quantitative assay.

2. ***Previous experiments have determined that there is no apparent difference in assay sensitivity when using HAE patient serum or normal human serum (see Complete Response Letter Question E.5.a). Due to limited availability of treatment naïve patient serum, we are planning on using normal human serum in these experiments. Is this approach acceptable?***

FDA Response:

Your approach is acceptable since patient sera matrix effects do not negatively impact the performance of this assay.

FDA Comment 3.a.(2):

To evaluate for cross-reactivity of anti-DX-88 antibodies with TFPI, perform studies to determine if human anti-DX-88 antibodies bind TFPI and perform epitope mapping of the human anti-DX-88 antibody response if binding is observed.

Dyax Questions:

1. ***What is the level of TFPI binding that would necessitate the epitope mapping?***

FDA Response:

Epitope mapping should be performed for any positive sample.

2. ***To clarify, is the epitope mapping to be performed on TFPI or DX-88?***

FDA Response:

Both neutralizing and non-neutralizing anti-DX88 antibodies should be tested for binding to TFPI. It would be informative to perform epitope mapping on both TFPI and DX-88 but that study is not required at this time.

3. ***Additionally, is epitope mapping using an*** (b) (4)

FDA Response:

Although the method proposed has limitations in that many (b) (4) this is the most common approach used for epitope mapping in both industry and academia. Based on clinical experience with DX88, (b) (4) would be sufficient to address our current concerns.

FDA comment 3.a.(3):

Develop and validate anti-DX-88 specific 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-DX-88 IgG antibodies.

Dyax Questions:

1. ***Since no commercially available positive control (PC) reagents are available, we would propose to continue using the*** (b) (4) ***reagent utilized in the current assay format. Is this approach acceptable?***

FDA Response:

Ideally, immunoaffinity purified DX-88-specific human IgE would be used, but since this doesn't appear to be feasible at this juncture, the (b) (4) reagent is acceptable as an initial approach provided that it is (b) (4) that would interfere with the assay. The assay validation results obtained should be confirmed using immunoaffinity purified DX-88-specific human IgE if sufficient quantities of such a sample become available.

2. ***Due to limited availability of treatment naïve patient serum, we are planning on using normal human serum in these experiments. Is this approach acceptable?***

FDA Response:

The approach is acceptable but the cut-point should be confirmed using patient sera to ensure against patient population specific matrix effects that could negatively impact assay performance.

If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Colette Jackson, Project Manager

Drafted: October 28, 2009

Initialed: Barnes/ October 28, 2009
Ragheb October 28, 2009
Kirshner/ October 28, 2009

Finalized: CCJ/ October 28, 2009

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: October 27, 2009

To: Nicole D'Auteuil	**From:** Colette Jackson
Company: Dyax	Division of Pulmonary and Allergy Products
Fax number:	**Fax number:** 301-796-9718
Phone number:	**Phone number:** 301-796-1230

Subject: BLA STN 125277 Product Information Request and Comments

Total no. of pages including cover: 3

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Document to be mailed: YES xNO

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BLA STN 125277
Kalbitor

OCT 27 2009

We are currently reviewing your BLA resubmission dated June 1, 2009, and we have the following comments and request for information.

1. In your June 1, 2009, response to our March 25, 2009, Complete Response letter you have provided information on your Inhibition Constance Ki assay. You have based the preliminary acceptance criteria on the validation data, four drug substance batches, and three drug product batches. However, in your release and stability table you have listed the specification as "TBD". This is not acceptable. Establish interim specifications with upper and lower limits.

2. For the SDS-PAGE gels [redacted] (b) (4)

3. You will be using two methods to measure sub-visible particles; the Single Particle Optical Sensing (SPOS) method and MicroFluid Imaging (MFI) method. However, in your release and stability table for the drug product you have listed the specification as "report results". This is not acceptable. Establish interim specifications for sub-visible particles.

4. You state that the identity of each batch of drug substance is determined by Western Blot at the contract manufacturing facility. However, going forward you will use [redacted] (b) (4) as the identity test. The [redacted] (b) (4) method is not a true identity test. The Western blot is a true identity test. Given that [redacted] (b) (4) will be used at a contract manufacturer, the profile of DX-88 has the potential of being similar to other products and therefore, it is unacceptable to change the identity test.

5. You provided the updated reference standard qualification protocol. As part of this protocol you have added the Inhibition Constance Ki assay to the list of assays. However, the suggested specification should also be sufficiently stringent to control for potential drift in the characteristics of the reference standard. Please tighten the specification for the Inhibition Constance Ki assay to control for this potential drift.

If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Colette Jackson, Project Manager

Drafted: October 26, 2009

Initialed: Barnes/ October 27, 2009
Lee/ October 27, 2009

Finalized: CCJ/ October 27, 2009

Filename: 125277 October 2009 product fax.doc

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: October 16, 2009

To: Nicole D'Auteuil	**From:** Colette Jackson
Company: AstraZeneca	Division of Pulmonary and Allergy Products
Fax number:	**Fax number:** 301-796-9718
Phone number:	**Phone number:** 301-796-1230

Subject: BLA 125277 FDA Proposed Labeling and Comments

Total no. of pages including cover:

Comments:

Document to be mailed: YES xNO

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BLA 125277
Kalbitor

OCT 16 2009

Please refer to your June 1, 2009, biologics license application (BLA) resubmission for Kalbitor (ecallantide). We have the following comments and labeling recommendations for the proposed Package Insert, Medication Guide, and the carton and container labeling. The FDA-proposed insertions are underlined and deletions are in strike-out. These comments are not all-inclusive and we may have additional comments. Submit revised draft labeling incorporating the changes outlined in our enclosed labeling by COB October 26, 2009. In addition, we have outlined potential post-marketing requirements. We request your response to these requirements by COB October 30, 2009.

1. The following comments pertain to the Package Insert.

   a. The following comments pertain to the Highlights section.

      (1) Reference to the KALBITOR CASE program has been removed.

      (2) The skin testing and graded challenge procedures are considered investigational and have been removed from the label.

      (3) The indications statement has been simplified and revised to include the recommended age range.

      (4) The dosage and administration instructions regarding a second dose within a 24-hour period have been clarified. Recommendations regarding administration in an appropriate healthcare setting have also been added.

      (5) A statement cautioning users about the similarity between certain acute HAE symptoms and hypersensitivity has been added.

   b. The following comments pertain to Section 2.2, Dosage and Administration, Administration Instructions.

      (1) Provide the recommended needle size for subcutaneous injection.

      (2) Provide more detail on the selection of an appropriate injection site and the need for site rotation, if any.

      (3) Describe the administration of a second dose, including selection of an appropriate administration site.

   c. The following comments pertain to Section 5.1, Warnings and Precautions, Hypersensitivity Reactions Including Anaphylaxis.

(1) The anaphylaxis rate of 3.9% is based on 10 patients identified from Analysis Population 1.1 meeting diagnostic criteria for anaphylaxis as defined by the 2006 NIAID/NIH Joint Symposium on Anaphylaxis. Events from the rechallenge protocol and the cardiothoracic surgery development program are not included.

(2) The calculated rate of rash is based on patients reporting one or more of the following preferred terms after receipt of ecallantide: rash, rash macular, rash generalized, and rash erythematous.

(3) The calculated rate of pruritus is based on patients reporting one or more of the following preferred terms after receipt of ecallantide: pruritus, pruritus allergic, eye or ear pruritus, and pruritus generalized. Injection site pruritus was not included in this group but was included under injection site reactions.

(4) The calculated rate of urticaria is based on patients reporting one or more of the following preferred terms after receipt of ecallantide: urticaria, and urticaria localized.

d. The following comments pertain to Section 6.1, Adverse Reactions, Clinical Trials Experience.

(1) The calculated rate of injection site reactions is based on patients reporting one or more of the following preferred terms after receipt of ecallantide: injection site reaction, injection site pain, injection site pruritus, injection site irritation, injection site erythema, injection site urticaria, and injection bruising. Based on this grouping, in EDEMA4 and EDEMA3, there were 3 patients with injection site reactions compared to none in placebo. This information should be added to Table 1. For Analysis Population 1.1, injections site reactions were reported in 19 patients (7.4%).

(2) Rename Study 1 and Study 2 as EDEMA4 and EDEMA3 throughout the label.

(3) Revise Table 1 to present the pooled safety data from EDEMA3 and EDEMA4, rather than showing the trial data separately. Rank the adverse events in order of descending frequency. Combine the columns under each treatment group to show the number of patients and the percentage in parentheses [n(%)]. Round the percentages to the nearest whole numbers.

(4) The term, "tachycardia" should be used in the table instead of the term, "tachycardia NOS."

e. The following comments pertain to Section 14, Clinical Studies.

(1) Provide demographic information for the pooled EDEMA3 and EDEMA4 trials.

(2) Revise Table 2 to show the mean value of MSCS and TOS with 95% CI and p-values. Simplify the reported MSCS data values to one decimal place. Round the TOS values to the nearest whole number and do not include any decimal placed. Remove the Median, IQR, and SD. Include a footnote defining the abbreviations for MSCS and TOS.

(3) Information on medical intervention patterns has been included. Data from other secondary efficacy variables have been removed.

2. The following comments pertain to the proposed Carton and Container labeling

a. General Comments.

(1) Per 21 CFR 610.61, increase the prominence of the established name. The point size and typeface of the proper name shall be at least as prominent as the point size and typeface used in designating the trademark and trade name. The contrast in color value between the proper name and background shall be at least as great as the color value between the trademark and trade name and the background. Typography, layout, contrast, and other printing features shall not be used in a manner that will affect adversely the prominence of the proper name.

(2) Separate and relocate the dosage form and route of administration on the primary panel. Consider the following presentation:

Kalbitor
(ecallantide)
Injection
For Subcutaneous Use

b. The following comments pertain to the Container Label.

(1) Add a "Single use; discard unused portion" statement.

(2) Delete the graphic (circle containing the capital letter 'K') located immediately in front of the proprietary name (Kalbitor).

c. The following comments pertain to the Carton Labeling.

(1) To minimize distraction, relocate the graphic (circle containing the capital letter 'K') away from the product information. Alternatively, decrease its prominence.

(2) Add a net quantity statement (i.e. Net quantity: 3 vials).

(3) Delete the "30 mg" and "one dose" statements from the principal display panel.

(4) Increase the prominence of the product strength (10 mg/mL) by presenting it directly beneath the established name in a comparable font.

(5) List the single use statement separate from the strength and net quantity (e.g. single use; discard unused portion).

(6) Increase the prominence of the required medication guide statement by relocating it to the principal display panel.

(7) Increase the prominence of the storage requirements (e.g. keep refrigerated; do not freeze; protect from light).

(8) Add applicable agents or a reference to applicable agents to carton labels to comply with 21 CFR 610.61(l)(m)(o)(p)(q).

3. As discussed in the October 7, 2009, teleconference, the Agency has identified several issues that will need to be addressed. If Kalbitor is approved and these issues have not been addressed, these may become post-marketing requirements. We request that you acknowledge your agreement to perform the following studies and submit a timetable for completion of each. The timetable should include the following: protocol submission date (if applicable), study completion date (if applicable), and final report submission date. Include a synopsis of how you plan to address each issue.

a. Immunoassays

(1) For the anti-DX-88 neutralizing antibody assay, establish the clinically relevant LLOQ, ULOQ, LOD, and cutpoint for this assay using immunoaffinity purified DX-88-specific human IgG.

(2) To evaluate for cross-reactivity of anti-DX-88 antibodies with TFPI, perform studies to determine if human anti-DX-88 antibodies bind TFPI and perform epitope mapping of the human anti-DX-88 antibody response if binding is observed.

(3) Develop and validate anti-DX-88 specific 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-DX-88 IgG antibodies

b. Proposed long-term safety study (DX-88/24).

(1) Specify a separate analysis for adverse events related to disordered coagulation, both hypocoagulability and hypercoagulability.

(2) Revise the protocol to include a detailed description of the skin testing and graded challenge procedures that will be used in patients with evidence of clinical hypersensitivity who consent to undergo these procedures.

(3) We recommend skin testing at baseline and follow-up and follow-up IgE testing in a subset of patients without evidence of clinical hypersensitivity to provide further information on the positive and negative predictive values of these tests.

c. Carcinogenicity study

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.

If there are any questions, please contact Ms. Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

/Colette Jackson/
Colette Jackson
Senior Regulatory Health Project Manager

Enclosure: Recommendations to the Package Insert and Medication Guide

Drafted: CCJ/ October 16, 2009
Initialed:

Barnes/ October 16 , 2009
Limb// October 16, 2009
Seymour/ October 16, 2009

Finalized: CCJ/ October 16, 2009

Filename: 125277 October 2009 Labeling fax.doc

15 pp withheld immediately following this page as (b)(4) draft labeling.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125277/0

INFORMATION REQUEST

Dyax Corp
300 Technology Square
Cambridge, MA 02139

OCT 16 2009

Attention: Nicole D'Auteuil
Senior Director, Regulatory Affairs

Dear Ms. D'Auteuil:

This letter is in regard to your biologics license application submitted under Section 351 of the Public Health Service Act for Kalbitor (ecallantide) Injection.

We also refer to our complete response letter dated March 25, 2009, and your resubmission dated June 1, 2009, that included your proposed Risk Evaluation and Mitigation Strategy (REMS).

In our March 25, 2009, letter we notified you that a REMS was required for Kalbitor (ecallantide) to ensure that the benefits of the drug outweigh the risk of anaphylaxis following treatment. As part of the REMS, we indicated that the REMS must include a Medication Guide to ensure patients' safe and effective use of the drug, a communication plan targeted to healthcare providers to support implementation of the elements of your REMS, elements to assure safe use to mitigate a specific serious risk listed in the labeling (anaphylaxis) an implementation system, and a timetable for assessment of the REMS.

We have completed our review of your proposed REMS as described in your submission dated June 1, 2009. Although we believe a REMS is necessary to ensure the safe use of Kalbitor (ecallantide), upon further consideration, we do not believe that a restricted program with elements to assure safe use is necessary to ensure the benefits of the drug outweigh the risks of anaphylaxis. The risk of hypersensitivity reactions is not unique to Kalbitor (ecallantide) and is an expected adverse event for a foreign protein-derived biologic product. Other drug products with a similar risk of anaphylaxis have not exhibited the need for a restricted program with elements to assure safe use, and there is no evidence to suggest that the nature of hypersensitivity reactions associated with Kalbitor (ecallantide) differs from more well-known drug-induced hypersensitivity reactions. While there remains some concern that the clinical signs and symptoms of hereditary angioedema (HAE) may overlap with the signs of drug hypersensitivity and cause confusion for healthcare providers and patients, if Kalbitor (ecallantide) is approved, the FDA-approved labeling for Kalbitor (ecallantide) will recommend that the drug be administered in a setting that is equipped to manage anaphylaxis.

In addition, we have determined that we cannot conclude that the proposed elements to assure safe use would mitigate the risk of anaphylaxis, and they could hinder patient access to Kalbitor (ecallantide). Specifically, the proposed elements to assure safe use could interfere with the availability of Kalbitor (ecallantide) and increase the risks of a delay of therapy. Because acute attacks of HAE are potentially serious and life threatening, a delay or limitation in access is not desirable.

Therefore, although we continue to believe that a REMS is necessary to ensure the benefits of Kalbitor (ecallantide) outweigh its risks, we have concluded that it is not necessary to include elements to assure safe use as part of the REMS. However, a Medication Guide and communication plan remain necessary to communicate important information to patients and providers about the unique characteristic of the risk – anaphylaxis – that may overlap with presenting symptoms of the disease. The communication plan must include at a minimum the following:

- A Dear Healthcare Provider Letter to be distributed at the time of first marketing. Your communication plan should state specifically the types and specialties of healthcare providers to which the letters will be directed. These providers should include non-prescribers in specialties likely to treat HAE patients, such as emergency room providers.
- Dissemination of information about the need for distinguishing between hypersensitivity reactions and lack of product efficacy (persistent HAE symptoms).
- A schedule for when and how these letters/materials are to be distributed at the time Kalbitor (ecallantide) is approved, and at specified intervals thereafter, if this application is approved.

You should submit a revision to the proposed REMS and REMS supporting document included in your June 1, 2009, submission that includes the Medication Guide and communication plan and timetable for submission of assessments described in our March 25, 2009, letter. You should remove the elements to assure safe use and the implementation system from your proposed REMS, as they are no longer part of the REMS.

Updates to the REMS supporting document may be included in a new document that references the previous REMS supporting document submission for unchanged portions of the REMS, or updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted.

Prominently identify subsequent submissions related to the Proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

BLA 125277
Proposed REMS-Amendment

If you have any questions, please call Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Sincerely,

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

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: August 5, 2009

To: Nicole D'Auteuil	**From:** Colette Jackson
Company: Dyax	Division of Pulmonary and Allergy Products
Fax number:	**Fax number:** 301-796-9718
Phone number:	**Phone number:** 301-796-1230

Subject: BLA STN 125277 Comments

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Comments:

Document to be mailed: YES xNO

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BLA STN 125277
Kalbitor

AUG 5 2009

We are reviewing your biologics licensing application (BLA) resubmission dated June 1, 2009. We also refer to your submission dated July 21, 2009. We have the following comments. Please submit the requested information, by COB August 12, 2009, in order to facilitate our review of your BLA resubmission.

1. In your July 21, 2009 submission, you provided information regarding your skin test and test dose procedure. Please clarify if there were any validation studies performed for the skin test procedure described in this submission. If so, please provide those studies including the positive and negative predictive values for the test. If not, please provide your plans to obtain these values.

2. Upon preliminary review of your Medication Guide, your readability scores are not acceptable. The proposed Medication Guide has a Flesch Kincaid Grade level of **12.2** and a Flesch Reading Ease score of **34.0%**. To enhance patient comprehension, patient directed materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). You should modify the proposed Medication Guide using patient-friendly language and improve on the readability scores.

3. There are some standard Medication Guide sections and content that are missing and should be added, including:

   What is Kalbitor?

   How should I take Kalbitor? (In this case ***How will I receive Kalbitor ?*** may be more appropriate wording)

   What should I avoid while taking Kalbitor? (if it applicable)

   What are the possible side effects of Kalbitor? This section must include the required verbatim side effect language:

   "Call your doctor for advice about side effects. You may report side effects to FDA at 1-800-FDA-1088."

   The section "***General information about Kalbitor***" should be revised. The following required verbatim statement is missing:

   > *"Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide."*

   Refer to the Medication Guide Regulations specified in 21 CFR 208 when revising your proposed Medication Guide.

4. Indicate how the label is affixed to the vial and where the visual area of inspection is located as per 21 CFR 610.60 (e).

5. Relocate the license number to the following presentation per 610.61(b).

   Dyax Corp.
   300 Technology Square
   Cambridge, MA 02139
   License: XXXX

6. Add the statement "*Do Not Freeze*" capitalized and in bold type per 21 CFR 610.61(i) on all labeling.

7. Add applicable agents or a reference to applicable agents to carton labels to comply with 21 CFR 610.61(l)(m)(o)(p)(q).

8. Add the statement "*No U.S. standard of potency*" to the carton label to comply with 21 CFR 610.61(r).

9. Relocate the route of administration and add the dosage form to the primary panel. Consider the following presentation:

   Kalbitor
   (ecallantide)
   Injection
   For Subcutaneous Use
   10mg/mL

10. Add the statement, "*Dispense the enclosed Medication Guide to each patient*" to the carton per 21 CFR 610.60.

11. Please provide font size configurations for the proprietary and established names on all carton and container labels.

12. Please consider relocating the NDC number to the top third of the primary display panel of the carton for improved readability and consistency with other prescription products.

13. The following comments pertain to the Package Insert.
    a. Please list the names of all inactive ingredients in alphabetical order in the "**DESCRIPTION**" section as per USPC Official 5/1/09-8/1/09, USP 32/NF27, <1091> Labeling of Inactive Ingredients.

b. Please indicate that the ecallantide is a sterile product in the **"DESCRIPTION"** section as per 21 CFR 201.57(12)(D),

Be advised that these labeling changes are not the Agency's final recommendations and that additional labeling changes will be forthcoming as the label continues to be reviewed.

If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Colette Jackson, Project Manager

Drafted: July 28, 2009

Initialed: Barnes/ July 31, 2009
Ragheb August 5, 2009
Rains/ August 5, 2009
Limb/ August 3, 2009
Seymour/ August 4, 2009

Finalized: CCJ/ August 5, 2009

Filename: 125277 July 2009 product and drisk fax.doc

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125277/0

Dyax Corporation
300 Technology Square
Cambridge, MA 02139

JUN 16 2009

Attention: Nicole D'Auteuil
Senior Director, Regulatory Affairs

Dear Ms. D'Auteuil:

Please refer to your biologics license application (BLA) submitted under the Public Health Service Act for Kalbitor (ecallantide) Injection.

We also refer to the meeting held on May 14, 2009, between representatives of your firm and this agency. A copy of the official minutes of the meeting is attached for your information.

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, please contact me at (301) 796-1230.

Sincerely yours,

Colette Jackson

Colette Jackson
Senior Regulatory Project Manager
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Meeting Summary

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type:	Type A
Meeting Category:	Advice
Meeting Date and Time:	May 14, 2009, 4 PM - 5 PM
Meeting Location:	WO22, Conference Room 1419
Application Number:	BLA STN 125277
Product Name:	Kalbitor (ecallantide)
Received Briefing Package:	April 29, 2009
Sponsor Name:	Dyax Corporation
Meeting Requestor:	Nicole D'Auteuil Director, Regulatory Affairs
Meeting Chair:	Badrul A. Chowdhury, M.D., Ph.D. Division Director, Division of Pulmonary and Allergy Products
Meeting Recorder:	Colette Jackson Regulatory Health Project Manager

Meeting Attendees:

FDA Attendees:

Office of Drug Evaluation II, Division of Pulmonary and Allergy Products

Badrul A. Chowdhury, M.D., Ph.D., Division Director

Sally Seymour, M.D., Deputy Director for Safety

Susan Limb, M.D., Clinical Reviewer

Colette Jackson, Regulatory Health Project Manager

Ladan Jafari, Safety Project Manager

Office of Biostatistics

Dongmei Liu, Ph.D., Statistical Reviewer

Office of Clinical Pharmacology

Sally Choe, Ph.D., Acting Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 2

Yun Xu, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 2

Office of Biotechnology Products

Kathy Lee, M.S., Product Quality Reviewer, Division of Therapeutic Proteins

Susan Kirshner, Ph.D., Product Quality Team Leader

Veerasamy Ravichandran, Ph.D., Product Quality Reviewer, Division of Therapeutic Proteins

Jack Ragheb, M.D., Product Immunogenicity Reviewer, Division of Therapeutic Proteins

Office of Compliance

Anastasia Lolas., M.S., Microbiologist, Biotech Manufacturing Team, Division of Manufacturing and Product Quality

Laura Dillon, RPM, Biotech Manufacturing Team, Division of Manufacturing and Product Quality

Shawn Gould, Division of Manufacturing and Product Quality

Office of Surveillance and Epidemiology

Douglas Pham, Pharm.D., J.D., Drug Risk Management Analyst, Division of Risk Management

Claudia Karwoski, Pharm.D., Acting Director, Division of Risk Management

Elizabeth Donohoe, M.D., Drug Risk Management Analyst, Division of Risk Management

Sean Bradley, Project Management, OSE IO

Dyax Attendees:

Nicole D'Auteuil, Senior Director, Regulatory Affairs

Aurelie Grienenberger, Ph.D., Director, Regulatory Affairs

Michele Miller, Distribution Expert

Bill Pulman, M.D., Ph.D., Executive Vice President and Chief Development Officer

Gustav Christensen, President & CEO

(b) (4)

(b) (4)

1.0 BACKGROUND

Dyax sent in a meeting request dated April 6, 2009, to discuss the March 25, 2009, Complete Response Letter from the Agency. The briefing package was received on April 29, 2009. Upon review of the briefing package, the Division responded to Dyax's questions via fax on May 13, 2009. The content of that fax is printed below. Any discussion that took place at the meeting is captured directly under the relevant original response in Section 2.0, including any changes in our original position. Dyax's question is in ***bold italics***; FDA's response is in *italics*; discussion is in normal font.

2.0 DISCUSSION

Introductory Comment:

The general plan and goals of the proposed REMS appear reasonable but will require further detail and justification for each element. Your submission should explain how each element will contribute to the safe use of ecallantide and support the stated goals of the program. The contribution of certain specific elements, such as the certification of hospital pharmacists, is unclear from the materials provided, and details regarding operationalizing this element are lacking. Provide complete details for each element of the REMS, including copies of all educational materials and forms and a detailed description of each operational step, such as drug distribution and storage and management of registry data. In addition, we have concerns about the proposed name of the REMS program, (b) (4)*." We request that the REMS program be named in such a manner so that its purpose is apparent to healthcare providers and patients. The use of the word* (b) (4) *may be promotional in nature.*

5.4.1 REMS Questions

Question 5.4.1.1: ***Is FDA in agreement with the goals and objectives of the KALBITOR REMS as stated in Section 6.2 and in the draft proposed REMS in Attachment 1?***

FDA Response:

The proposed goals and objectives in this draft REMS appear satisfactory, but further review will need to be conducted upon receipt of a REMS submission. Language used

should be clear and concise in describing the ultimate REMS goal of mitigating the risks associated with Kalbitor, while listing specific objectives for achieving that goal.

Question 5.4.1.2: ***Does the draft REMS address the REMS requirements described in the Complete Response letter?***

FDA Response:

The draft REMS does address the requirements described in the Complete Response letter. However, further review is required to determine whether the proposed REMS elements are an effective method to satisfy and meet the goals of this REMS program.

Some preliminary concerns of this draft REMS include, but are not limited to the following:

- *The verification process of an enrolled patient in the* (b) (4) *by an administration site. In your description of the verification process, provide the complete operational details of the process, e.g. how support staff at an administration site will know to trigger the verification process for an individual patient and administer drug only to confirmed patients. Explain how this process can be completed in a timely manner in the setting of an acute HAE attack.*

- *The role of certified hospital pharmacists in the* (b) (4)

The REMS Supporting Document should provide procedural details about these elements and how these elements will mitigate the risks associated with ecallantide.

To ensure an effective review of a REMS submission, please include all proposed enrollment kit materials and information, Dear Healthcare Provider Letters, Medication Guide, and screen shots of a proposed website.

Discussion:

Dyax opened the discussion noting that they intend to respond to all of the deficiencies outlined in the FDA's March 25, 2009, Complete Response (CR) letter. The resubmission is planned for the end of May 2009. Dyax stated they intend to submit additional information with the resubmission that will clarify the patient verification process for eligibility to receive the drug and the role of the hospital pharmacy. Dyax has selected a pharmacy distributor which will be the sole dispensary of the drug product and will be responsible for the input of patient data. Both hospitals and prescribers will contact the distributor to verify if the patient is eligible. The distributor will be available 24 hours a day and will make sure that the eligibility verification process takes less than 15 minutes. The FDA suggested Dyax provide as much detail as possible in the resubmission. The FDA asked Dyax to define the eligibility criteria. Dyax stated that the call center will walk the health care practitioner through the process in order to assure the patient meets the eligibility criteria. The FDA noted that the criteria that will be used to

determine whether a patient is eligible for treatment with Kalbitor should be included in the supporting document of the REMS.

Dyax stated that there will be designated and certified hospital pharmacists at each administration site and precautions will be taken to make sure that the drug is not sent to an unapproved, unenrolled site. The FDA noted that the intended administration will most likely take place in the hospital emergency room, and asked Dyax who would be responsible for contacting the call center for patient eligibility. Dyax stated they will ensure that the REMS document includes this level of detail in the resubmission.

The FDA informed Dyax that a REMS typically takes months for review and this application will most likely take the full 6 months for review. The FDA suggested Dyax provide as much detail as possible to facilitate review.

Question 5.4.1.3: ***In the Complete Response letter, the FDA stated that the REMS implementation system "must also include a plan to address any findings of inadequate implementation of these elements to assure safe use" and that "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 element should be modified". Dyax seeks the agency's guidance on the approach outlined in Section 6.3.4 for addressing these requirements.***

FDA Response:

The proposed Implementation Plan appears to be appropriate but lacks substantial detail. Detailed descriptions will be needed to explain your mechanisms for correcting non-compliant administration sites or procedures for measuring/auditing the compliance of certified healthcare providers in the Kalbitor KARE program. For example, further details of the proposed corrective action and preventative action (CAPA) plan will be required.

Discussion:

Dyax stated they intend to include a detailed description of their monitoring program and asked the FDA to clarify the review process. The FDA noted that usually communications are sent to request information or obtain clarification from the sponsor. The FDA strongly suggests Dyax provide a prompt response when communications are sent during the review cycle.

Question 5.4.1.4: ***As an element to assure safe use, each patient is required to enroll in the mandatory product use registry prior to treatment. The registry includes the collection of patient demographic and baseline information prior to treatment and treatment information, including occurrence of anaphylaxis, following KALBITOR administration (as described in Section C.5 of the proposed REMS). Does the FDA require other type of information to be collected in the patient product use registry?***

FDA Response:

A full review of the REMS submission is necessary to determine what types of information should be collected from patients upon enrollment into the program.

Question 5.4.1.5: ***The BLA resubmission will include a description of the product use registry in the proposed REMS and the draft data collection forms for the registry. Does the FDA require any further information regarding the registry to be included in the resubmission?***

FDA Response:

We cannot provide a response to this question until we have conducted a full review of the REMS submission. Please note that the submitted forms and other registry instruments should be formatted mock-ups.

Discussion:

Dyax stated that they intend to provide a description of the registry protocol and data elements and asked the FDA if any other information/items are needed (e.g., mockups). The FDA stated that the data collection forms, data report forms, and collection frequency would be required. Dyax asked if screen shots could be submitted since it is an electronic process and FDA said that forms were preferred but screenshots could also be submitted.

Question 5.4.1.6: ***In the Complete Response letter, the FDA stated that the proposed REMS submission must include two parts: a "Proposed REMS" and a "REMS Supporting Document." The draft proposed REMS is provided in Attachment 1. Section 6 of the meeting package provides the basis for the REMS Supporting Document. Dyax is seeking guidance around the appropriate level of detail for each document. The following information is planned to be included in each document. Is this approach acceptable?***

FDA Response:

Pending full review of the REMS submission, your approach in developing the proposed REMS and the REMS Supporting Document appears appropriate.

The proposed REMS should include concise information describing the goal(s) of the REMS and the REMS element(s) proposed for inclusion in the approved REMS for the specified product. All materials that are included as part of the REMS (e.g., communication and education materials, enrollment forms, prescriber and patient agreements) should be appended to the proposed REMS. The REMS Supporting document should provide a thorough explanation of the elements of the REMS including a description of why particular elements and tools were chosen for the proposed REMS and how each particular element and tool will contribute to achieving the goals of the

REMS. It should also include details for how you plan to assess the REMS and the information that will be collected to make that assessment.

Discussion:

Dyax asked for clarification of the content of information required in the REMS document versus the supporting documentation. Dyax intends to respond to the items listed in the CR letter in hopes this will provide the required information. The FDA stated that Dyax needs to provide assurance that the patient understands the risk. This can be done by conducting a survey of patients and prescribers and is usually conducted separately from the enrollment process.

Question 5.4.1.7: ***Would the FDA clarify whether both documents or only the Proposed REMS becomes public in the event KALBITOR is approved?***

FDA Response:

The REMS and all appended documents will be made public upon approval by the FDA. The REMS Supporting Document will not be posted on the FDA website.

Discussion:

Dyax asked the FDA if the supporting document will be available to the public after approval and, if so, will proprietary information be redacted. The FDA informed Dyax that it is usual procedure to redact any proprietary information from any documents released from the Agency. The FDA suggested Dyax flag any sensitive information that they believe is proprietary.

Question 5.4.1.8: ***Please see the list of appendices in the proposed REMS located in the draft REMS in Attachment 1. Are any additional appendices or supporting documents required?***

FDA Response:

The items listed in Attachment 1 in your draft REMS appear to be appropriate, but may not be sufficient. Additional items may be needed upon review of your REMS submission.

5.4.2 Pediatric Question

Question 5.4.2.1: ***Section 7 provides a description of our pediatric resubmission plans. Does the FDA have any recommendations about the resubmission plan or for additional analyses?***

FDA Response:

We do not believe you have sufficient data at this time to support the proposed indication in pediatric patients down to 10 years of age. As a path forward, we suggest that you revise the proposed age range to 18 years and older and include a pediatric plan in your

Complete Response that details how you will continue to assess safety, efficacy, and pharmacokinetic parameters in patients 10 to 17 years of age.

In your previous submission, there were issues with the bio-analytical assays. The pharmacokinetic (PK) data are based on the bio-analytical assays, which is used to support the proposed dose in patients less than 18 years of age. You need to address the bio-analytical assay issues to ensure that the exposure data in this population are reliable and the appropriate dose in this population is assured. 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, to address our questions. 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 TGA Sciences. Therefore, you should resubmit the reports with required information. If any of the three bio-analytical assays are considered invalid, then the data generated from the invalid assay should not be included in the population pharmacokinetics analysis. In addition, since you need to evaluate more patients less than 18 years of age to support the indication in this age group, you should re-conduct the population pharmacokinetics analysis including the additional pediatric patients' data along with those from validated assay runs.

Discussion:

Dyax stated they will provide the required information on the PK assays and have updated reports. The assays have been validated and there is no impact on the population PK models. Dyax understands the FDA's concern regarding the adequacy of the data in the less than 18 years of age group and will provide a rationale in the resubmission to support approval down to the age of 10 years. Dyax noted that there is an unmet medical need, especially in the post-pubertal age group when the attacks present more frequently. Dyax acknowledges that of the 28 patients in the PK study, 98% of the patients are greater than 12 years of age. Dyax intends to continue to collect data for those 12 years of age and older using a registry.

The FDA noted that the meeting package did not contain any additional information, and that the proposed pediatric data in the resubmission were unlikely to be sufficient to support the proposed age range down to 10 years. The FDA advised Dyax to limit the indication to 18 years and older for the purposes of the resubmission and include a pediatric plan in the resubmission. The FDA stated that more safety and efficacy data in pediatric patients was required and could be obtained through a variety of study designs. A double-blind, placebo-controlled trial was not necessary. An open-label study with a reasonable, representative number of patients for each year of age proposed would be acceptable. These data, along with validated PK measurements in pediatric patients, could then form the basis for an efficacy supplement at a later date. The FDA recommended that a protocol be submitted under the IND with a request for FDA feedback.

5.4.3 Post-Marketing Requirements Questions

Question 5.4.3.1: ***Dyax proposes to conduct an open-label long-term safety study (observational study) that will collect data to evaluate anaphylaxis and type 1 as well as hypersensitivity reactions and immunogenicity and the consequences of seroconversion. Would the FDA comment on the acceptability of the study design to address these two post-marketing requirements?***

FDA Response:

We recommend that you include the proposed protocol for the long-term safety study in the Complete Response, so that we may provide feedback and facilitate the start of the long-term safety study in conjunction with the start of commercial marketing of ecallantide. The proposed protocol should include details on skin testing and rechallenge procedures. Based on the information provided, the general study design intended to evaluate hypersensitivity and immunogenicity with ecallantide appears reasonable. The study should refine the estimated risk of anaphylaxis and hypersensitivity reactions and assess the risk of other potential adverse events, such as hypercoagulability. The study should also monitor the long-term effects of seroconversion, relating antibody status to efficacy over time and safety. As part of the effort to achieve these study objectives, we expect that you will address the deficiencies regarding the immunoassays cited in the Complete Response letter, as well as refining skin test and rechallenge procedures that may be used to screen patients.

We suggest that the first 200 ecallantide-naïve patients enrolled in the (b) (4), *who consent to participate in the long-term safety study be enrolled. We also recommend that the long-term safety study include an arm of non-naïve patients who have been prior participants in the EDEMA studies. Since the long-term consequences of seroconversion and its effect on safety and efficacy remain unknown, these non-naïve patients are of interest given their longer duration of exposure.*

Discussion:

Dyax asked the FDA if they can conduct the clinical evaluation of the Type 1 hypersensitivity as a post marketing requirement. Dyax would submit a detailed protocol synopsis and then develop a full protocol. The FDA stated that the synopsis would need to be reviewed for its acceptability and discussions can take place during the review cycle.

Question 5.4.3.2: ***The protocol for the proposed open-label long-term safety study will be submitted to the FDA within 6 months of an approved application with study start to occur within approximately 1 year of an approved application, subject to protocol agreement with the FDA. To help us plan resources accordingly, could the FDA comment on the acceptability of these timings?***

FDA Response:

See the response to Question 5.4.3.1.

Question 5.4.3.3: ***In the Complete Response letter, the FDA specified a post-marketing requirement to study the effect of ecallantide on coagulation. Dyax believes that the body of data already generated provides adequate information and proposes to include a comprehensive description of coagulation data, including new analyses in the BLA resubmission. Would the FDA accept the resubmission containing these data in lieu of a commitment for a post-marketing study?***

FDA Response:

We agree that a separate clinical study of coagulation parameters is not needed at this time. We do expect in vitro assessment of potential cross-reactivity between ecallantide and TFPI, which may theoretically predispose patients to hypercoagulability, as well as ongoing monitoring for adverse events related to hyper- and hypocoagulability in the long-term safety study.

Additional Non-Clinical Comments:

As stated in the section of Post-marketing Requirements Under 505(o) of the Complete Response letter dated March 25, 2009, you are required to conduct a study in rats to evaluate the carcinogenic potential of Kalbitor (ecallantide) if your application is approved. Provide your plan to address the Post-Marketing Requirement in your BLA resubmission.

5.4.4 Regulatory Questions

Question 5.4.4.1: ***The resubmission will contain FDA Form 356h, 3397 (User Fee Cover), and 3674 (Certificate of Compliance). Can the FDA confirm that no other administrative form or certificate are needed as part of the BLA resubmission?***

FDA Response:

We agree that no other forms or certificates are required.

Question 5.4.4.2: ***The resubmission will contain a draft medication guide as part of the REMS and a revised carton and vial label. However, Dyax does not plan to submit a revised Full Prescribing Information at this time. We plan to submit the revised Full Prescribing Information following receipt of FDA comments to proposed labeling and REMS. Is this acceptable?***

FDA Response:

No, we expect that Full Prescribing Information be included with the resubmission.

Question 5.4.4.3: ***All FDA requirements in the Complete Response letter will be addressed in a question/response format as part of Module 1, as presented below.***

Module 1 Section	Title	Content in Resubmission
1.11.1	Quality Information Amendment	Responses to CMC items from Complete Response Letter
1.11.2	Safety Information Amendment	Safety Update
1.11.4	Multiple Module Information Amendments	Responses to items others than CMC, including: - report providing pediatric data to date - data package on the coagulation parameters
1.16	Risk Management Plans	Proposed REMS

In addition, the Module 3 and Module 2 Quality Overall Summary will be updated to include revised CMC information. Module 5 will be updated to include updated longitudinal patient profiles per the Safety Update and updated bio-analytical reports. Does the FDA agree with this plan for CTD document updates?

FDA Response:

Yes, this plan for CTD updates is acceptable.

5.4.5 Outstanding Business

Question 5.4.5.1: ***Dyax submitted 2 clarifying questions to the BLA pertaining to the requested sterility waiver and vial label text on 10 April 2009 (Sequence 032) and requested FDA written responses. At the time of submission the current meeting package, we have not received feedback and are seeking FDA input in the event that they are still outstanding at the time of the meeting. The Sequence 0031 cover letter containing the questions is provided in Attachment 2 for reference.***

Discussion:

CMC-Microbiology

The FDA responded to the April 10, 2009, submission on May 7, 2009, (see Attachment 1 under section 5.0). Dyax requested clarification of the requirement for (b) (4) and sent a simplified flow chart in via e-mail on May 13, 2009, for review (see Attachment 2). The FDA stated that during review of the BLA, it was thought that (b) was not being performed, thus we asked for a waiver request. It is now (4)

clear that Dyax is performing the (b) (4) and can continue to perform the test and meet CFR requirements, in which case no further information is needed.

However, (b) (4) is no longer required and can be waived. In this case, it would be preferable not to perform (b) (4) due to the possibility of introducing contamination during sampling. Dyax can choose to submit a waiver request for (b) (4)

CMC

Dyax referred to comment 8a listed in the CR letter (see Attachment 3) and asked the FDA if further validation information is required for the potency assay to include the specifications. Dyax stated to generate the data would take some time and requested that they submit the information 1 month after the resubmission if the data is required. The FDA stated that proposed specifications are required to evaluate the product and it is ideal for all information to be supplied at the time of resubmission. Dyax could provide specifications after a defined number of batches to provide some data to evaluate the product. If Dyax chooses to submit the information afterwards, it would need to be submitted within 1 month or less from the date of receipt of the resubmission.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

4.0 ACTION ITEMS

There were no action items identified during the meeting.

5.0 ATTACHMENTS AND HANDOUTS

Attachment #1- May 7, 2009, FDA Communication

Attachment #2- Sterility Testing Flowchart

Attachment #3- March 25, 2009, Complete Response Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125277/0

Dyax Corporation
300 Technology Square
Cambridge, MA 02139

JUN 5 2009

Attention: Nicole D'Auteuil
Senior Director, Regulatory Affairs

Dear Ms. D'Auteuil:

We have received your June 1, 2009, resubmission to your biologics license application (BLA) for Kalbitor (ecallantide) Injection on June 1, 2009.

We consider this a complete, class 2 response to our action letter. Therefore, the user fee goal date is December 1, 2009.

Please cite the NDA number listed above at the top of the page for any communications concerning this application. Address all communications concerning this BLA as follows:

U.S. Postal Service/ Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

If you have any questions, please contact me at (301) 796-1230.

Sincerely,

Colette Jackson
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: May 7, 2009

To: Nicole D'Auteuil	**From:** Colette Jackson
Company: Dyax	Division of Pulmonary and Allergy Products
Fax number:	**Fax number:** 301-796-9718
Phone number:	**Phone number:** 301-796-1230

Subject: BLA STN 125277 Comments on April 10, 2009, submission

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES xNO

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MAY 7 2009

BLA STN 125277
Kalbitor

We have reviewed your submission dated April 10, 2009, and we have the following responses to the questions (in ***bold italics***) posed in your submission.

<u>FDA requirement 6 (Quality)</u> – As provided for by 21 CFR 610.9, submit a formal request to waive the requirement for a (b) (4)

(b) (4)

We seek FDA guidance on the wording of the request for a waiver.

We propose to submit the request for waiver as part of Module 1, section 1.12.5. Please confirm that this is the appropriate location.

<u>FDA Response:</u>

There is no specific wording for requesting a waiver for the (b) (4) The waiver should include an appropriate rationale for not (b) (4) following (b) (4). It is acceptable to submit the waiver request in Module 1 of the submission. Alternatively, you can perform the bulk sterility test should you choose not to request the waiver.

<u>FDA requirement on labeling</u>: The carton and vial labels will need to be revised to state that the product is sterile. 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".

<u>Dyax Question 2:</u> Due to the small size of the vial label, we request that these statements only be included on the box label. Do you agree? If so, is a waiver request required?

<u>FDA Response:</u>

We agree that the Medication Guide statement can be included on the carton (box) label alone for this product due to the small size of the vial label. No waiver request is required. We do recommend that both the vial and box labels contain the word "sterile" because it affects handling of the product and additional precautions taken when a product is labeled as sterile.

If there are any questions, please contact Colette Jackson, Senior Regulatory Project Manager, at 301-796-1230.

Colette Jackson, Project Manager

1 pp withheld immediately following this page as (b)(4) CCI/TS.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

BLA ACKNOWLEDGEMENT

Our STN: BL 125277/0

Dyax Corporation
300 Technology Square
Cambridge, MA 02139

MAR 19 2009

Attention: Nicole D'Auteuil
Senior Director, Regulatory Affairs

Dear Ms. D'Auteuil:

We have received your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for the following:

Name of Biological Product: KALBITOR (ecallantide) Injection

Date of Application: September 23, 2008

Date of Receipt: September 23, 2008

Our Submission Tracking Number (STN): BL 125277/0

Proposed Use: Treatment of Hereditary Angioedema

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.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 22, 2008. If the application is filed, the user fee goal date will be March 25, 2009.

The BLA Submission Tracking Number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road

Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission.

If you have any questions, call me at (301) 796-1230.

Sincerely,

Colette Jackson
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 12, 2009

To: Nicole D'Auetueil	**From:** Colette Jackson
Company: Dyax	Division of Pulmonary and Allergy Products
Fax number:	**Fax number:** 301-796-9718
Phone number: 617-250-5770	**Phone number:** 301-796-1230

Subject: BLA STN 125277 February 11, 2009, Meeting Minutes

Total no. of pages including cover: 5

Comments:

Document to be mailed: YES xNO

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MEETING SUMMARY ENCLOSED

Our Reference: BLA STN 125277/0

Dyax Corporation
300 Technology Square
Cambridge, MA 02139

MAR 12 2009

Attention: Nicole D'Auteuil
Senior Director, Regulatory Affairs

Dear Ms. D'Auteuil:

Please refer to your biologics license application (BLA) for Kalbitor (ecallantide) and to the teleconference held on February 11, 2009, between representatives of your firm and this agency. A copy of our meeting minutes is attached for your information.

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

Please address all submissions to this application to:

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

If you have any questions, please contact me at (301) 796-1230.

Sincerely yours,

Colette Jackson
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

Enclosure: Meeting Summary

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF TELECON

DATE: February 11, 2009

APPLICATION NUMBER: BLA 125277

BETWEEN:

Bill Pullman, Chief Development Officer
Peggy Berry, Regulatory Affairs
Aurelie Grienenberger, Regulatory Affairs
Christine Redmond, Clinical Operations
Pat Horn, Medical Affairs
Mark Sawyer, Technical Operations
Chris TenHoor, Preclinical
Nicole D'Auteuil, Regulatory Affairs

Phone: 1-888-583-1346

Representing: Dyax Corporation

AND

Office of Drug Evaluation II, Division of Pulmonary and Allergy Products

Badrul A. Chowdhury, M.D., Ph.D., Division Director

Lydia Gilbert-McClain, M.D., Deputy Division Director

Susan Limb, M.D., Clinical Reviewer

Jean Wu, Ph.D., Pharmacology/Toxicology Reviewer

Timothy Robison, Ph.D., Pharmacology/Toxicology Reviewer

Colette Jackson, Regulatory Health Project Manager

Office of Clinical Pharmacology

Wei Qiu, Ph.D., Acting Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 2

Yun Xu, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 2

Office of Biostatistics

Dongmei Liu, Ph.D., Statistical Reviewer

Qian Li, Ph.D., Statistical Team Leader

Office of Safety Evaluation, Division of Risk Management

Suzanne Berkmann, PharmD, Senior Risk Management Analyst and acting Team Leader

Elizabeth Donohoe, M.D., Risk Management Analyst

SUBJECT OF PHONE CONVERSATION: BLA 125277

Dyax Corporation sent in BLA 125277 on September 23, 2008. An Advisory Committee meeting was held for this application on February 4, 2009. The Division requested to speak with Dyax to discuss the status of their BLA application.

The Division referred to the February 4, 2009, Advisory Committee (AC) meeting, noting that it was a productive meeting which generated very useful information. The Division acknowledges the AC advice as shown by the votes and comments given to the public.

The Division referred to the Risk Mitigation Strategies proposed by Dyax at the AC meeting which acknowledged the risk of anaphylaxis and proposed how the safety risk should be managed. The safe use plan presented at the AC meeting was more extensive than the proposed risk mitigation strategies described in the BLA. The Division explained that the Agency will need to understand all the elements and the full operational details of the Risk Mitigation Strategies. The Division advised Dyax to submit an official Risk Evaluation Mitigation Strategies (REMS) plan for review. The Division will provide the REMS template to Dyax. Dyax will need to complete the template, append all necessary and proposed materials, along with the Supporting Document and submit it to the BLA. Upon submission of the REMS, the Division of Risk Management will review the REMS, in conjunction with the DPAP and other pertinent Divisions within CDER. The Division explained that the Agency's internal processes required to review and approve a REMS may take several months. Given that

this application has a March 23, 2009, PDUFA date, completing the REMS review within this review cycle will be extremely difficult. Also, given the need for a REMS, labeling review and discussions cannot be efficiently conducted at this time.

Dyax asked what level of detail is needed for a REMS. The Division suggested that Dyax address all of the elements outlined in the REMS template, providing as much detail as possible. The Division of Risk Management suggested Dyax go to the Drugs@FDA link on www.fda.gov to look at prior approval letters which contain REMS and gave the examples of NPLATE and PROMACTA, both recently approved for idiopathic thrombocytopenia purpura. This should direct Dyax to the level of detail necessary to provide for a REMS submission. The Division also requested that Dyax include detailed process information, on how the program will be operationalized, for example, the steps taken when a patient has an attack. Dyax needs to make sure that the information presented at the AC and to the public as to how to address safety needs is outlined thoroughly in the REMS submission.

Dyax asked if the educational materials are required with the proposed REMS document. The Division stated that actual educational materials are needed and acknowledged that the educational materials may require revision based on labeling negotiations. The Division asked Dyax to provide a comprehensive package to facilitate the ease of review. The actual time needed to review the REMS is affected by the quality of the REMS submitted. Therefore, DYAX should endeavor to submit a document that is complete. Dyax stated they understand the need for a complete and comprehensive package and they will discuss this internally and get back to the Agency with a timeline for submission.

The Division noted that the review is still ongoing, but that the Division will not extend the clock for this application. Dyax was advised to close out any open issues (i.e., information request items) with the Agency. The analysis and validity of the pharmacokinetic and immunogenicity assays are important issues that have yet to be resolved. Dyax referred to the February 10, 2009, facsimile sent by the Agency, stating that they will have to address the items outlined in the fax in separate, partial response submissions. The Division stated this is acceptable, but suggested items 1a and 1b be sent as soon as possible. Dyax stated they will make this a priority and provide the submission in a timely manner. The Division also asked Dyax to submit Clinical Pharmacology information in response to the December 4, 2008, facsimile sent to Dyax. The Agency requested the LLOQ QC and calibration curve information for all the in-study bioanalytical reports from (b) (4). A summary table was submitted but the Agency requires Dyax to resubmit in-study bioanalytical reports with the information mentioned above. Dyax stated they will amend the bioanalytical reports as soon as possible and provide them to the Agency.

Colette Jackson

Senior Regulatory Health Project Manager

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: February 10, 2009

To: Nicole D'Auteuil	**From:** Colette Jackson
Company: Dyax	Division of Pulmonary and Allergy Products
Fax number:	**Fax number:** 301-796-9718
Phone number:	**Phone number:** 301-796-1230

Subject: BLA STN 125277 Comments

Total no. of pages including cover: 6

Comments:

Document to be mailed: YES xNO

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BLA STN 125277 FEB 10 2009
Kalbitor

We are reviewing your biologics licensing application (BLA) submission dated September 23, 2008. We also acknowledge your submissions dated December 19, and 31, 2008, and January 23, and 27, 2009. We have identified the following possible issues. Please submit the requested information, by COB February 12, 2009, in order to facilitate our review of your BLA.

1. Please provide the following:

   a. Updated longitudinal patient profiles including DX88/19 patients.

   b. Updated adverse event table for Analysis Population I plus the DX-88/19 patients included in the safety update dated December 19, 2008.

   c. Updated Kaplan Meier analysis of seroconversion including the DX-88/19 patients.

   d. Updated antibody-adverse event analysis including the DX-88/19 patients.

   e. Change in MSCS for EDEMA3 and EDEMA4 recalculated as the arithmetic mean for 3 possible symptom complexes instead of 5. These 3 complexes would be: abdominal/GI, internal head/neck, and peripheral (external head/neck, genital/buttocks, and cutaneous grouped together).

   f. At the February 4, 2009, Advisory Committee Meeting, you presented a slide which showed the Change in MSCS and TOS as a function of time from attack onset to drug administration. Please provide a copy of these analyses for EDEMA3, EDEMA4, and EDEMA4 pre- and post-sample size change.

   g. Provide an analysis of the primary efficacy results as a function of the lowest historical C1-INH functional level and lowest historical C4 level.

   h. Provide an analysis of the primary efficacy results as a function of Type I versus Type II HAE.

2. The approaches for the new studies outlined in your submission dated January 27, 2009, appear adequate. We do not have any strong recommendations regarding the prioritization of these studies, however, you may want to resolve the issues associated with the ELISA for DX-88 in serum first, as they may impact the results of your PK studies. We recognize that these studies are unlikely to be completed in their entirety before the PDUFA date, but suggest that you include timelines for completion and submission of this information.

3. As Genzyme is unable to provide information on the (b) (4) of the (b) (4) used in the IgE assays, please characterize the chimeric positive controls used in the DX-88 and P. pastoris IgE assays. Such characterization should include, but is not limited to, the molecular weight, the ratio of (b) (4) to (b) (4), the level of (b) (4) or (b) (4) in the preparation, and the presence of any DX-88 or P. pastoris host cell protein in the positive controls if the controls were immunoaffinity purified.

4. For all the PK and Phase 3 immunoassays (all IgE and non-IgE assays) please provide a table indicating the DX-88 lot number used in the assay, the amount of P. pastoris host cell protein present in that lot, and the assay(s) in which the lot was used.

5. The following comments pertain to your Neutralization Assay:
   a. As a clarification of comment 15.a.2 in our communication dated January 16, 2009, we recommend that (b) (4) This could be determined for the (b) (4) and the (b) (4).

   b. It is unclear to us why you do not include sample containing serum in your (b) (4) Please provide your rationale.

   c. In your submission dated December 31, 2008, which was in response to our comment 17.a.2 of our November 20, 2008, filing letter, you state that the NC is (b) (4) If this is the case, it is not indicated in method TLIAM-0060.03. Please clarify.

6. Based on your response submitted on Jan. 23, 2009, it looks like there were 3 issues to be considered in data imputation: emerging symptom complexes, medical intervention, and SUAC failure. With this understanding, we find that the results provided in Table 7 in your response submitted in Jan. 13, 2009 (provided in appendix) are inconsistent in using imputation rules.

   To clarify the inconsistency, please provide update on data imputation analyses using the table shell we provide below. Please fill in every cell in the table and do not leave any blanks. Please also submit the data sets you use to do the analysis.

P values using different approaches to data imputation.

	Imputation with SUAC failure						Imputation without SUAC failure					
	Based on rule specified in BLA submission			Based on rule specified by FDA			Based on rule specified in BLA submission			Based on rule specified by FDA		
	E3-As TX	E3-ITT	E4 ITT	E3-As TX	E3-ITT	E4 ITT	E3-As TX	E3-ITT	E4 ITT	E3-As TX	E3-ITT	E4 ITT
Change from baseline in MSCS score at 4 hours												

No imputation												
With imputation for emerging symptom complexes												
With imputation for emerging symptom complexes and medical intervention												
Change from baseline in MSCS score at 24 hours												
No imputation												
With imputation for emerging symptom complexes												
With imputation for emerging symptom complexes and medical intervention												
TOS at 4 hours												
No imputation												
With imputation for emerging symptom complexes												
With imputation												

for emerging symptom complexes and medical intervention												
TOS at 24 hours												
No imputation												
With imputation for emerging symptom complexes												
With imputation for emerging symptom complexes and medical intervention												

Appendix: Response submitted on Jan. 13, 2009

Table 7. P-Values Using Different Approaches to Data Handling for Emerging Symptom Complexes and Medical Intervention in EDEMA3-DB and EDEMA4

	P-Value for New Imputation Analyses Per FDA Request of 7 January 2009			P-Value for Analyses Using Previous Imputations		
	E3-As TX	E3-ITT	E4 ITT	E3-As TX[a]	E3-ITT[a]	E4 ITT[b]
Change from baseline in MSCS score at 4 hours						
No imputation	--	--	--	0.041	0.096	0.010
With imputation for emerging symptom complexes	0.035	0.083	0.006	--	--	0.001
With imputation for emerging symptom complexes and medical intervention	0.162	0.279	0.372	0.044	0.094	<0.001
Change from baseline in MSCS score at 24 hours						
No imputation	--	--	--	0.484[c]	0.484[c]	0.039
With imputation for emerging symptom complexes	0.490	0.490	0.019	--	--	0.005
With imputation for emerging symptom complexes and medical intervention	0.437	0.437	0.132	0.142	0.142	0.001
TOS at 4 hours						
No imputation	--	--	--	0.045	0.138	0.003
With imputation for emerging symptom complexes	0.046	0.139	0.002	--	--	0.002
With imputation for emerging symptom complexes and medical intervention	0.146	0.343	0.143	0.037	0.10	<0.001
TOS at 24 hours						
No imputations	--	--	--	0.360[c]	0.360[c]	0.029
With new imputation for emerging symptom complexes	0.379	0.379	0.010	--	--	0.019
With imputation for emerging symptom complexes and medical intervention	0.994	0.994	0.046	0.044	0.044	0.041

[a]In EDEMA3-DB, imputations for emerging symptoms complexes and medical intervention were prospectively described in the study Statistical Analysis Plan, Section 7.0. In addition, post-hoc sensitivity analyses were performed without using data imputations. These analyses were reported in the Summary of Clinical Efficacy (BLA Section 2.7.3). The EDEMA3-DB 24-hour unimputed analyses were not performed for the BLA but are included herein (see footnote [c]).
[b]In EDEMA4, the primary analysis did not allow imputations. Sensitivity analyses using imputations for emerging symptoms and for emerging symptoms + medical intervention were defined in the study, as stated in Section 9.7.3.1.1 of the EDEMA4 CSR.
[c]Analyses for EDEMA3-DB TOS and change in MSCS score at 24 hours without imputations were conducted post-hoc for comparative purposes and have not previously been submitted to the BLA. The tabular results are provided in Attachment B.

If there are any questions, please contact Colette Jackson, Regulatory Health Project Manager, at 301-796-1230.

Colette Jackson, Project Manager

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: January 16, 2009

To: Nicole D'Auteuil	**From:** Colette Jackson
Company: Dyax	Division of Pulmonary and Allergy Products
Fax number:	**Fax number:** 301-796-9718
Phone number:	**Phone number:** 301-796-1230
Subject: BLA STN 125277 Comments	
Total no. of pages including cover:	
Comments:	

Document to be mailed: YES xNO

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BLA STN 125277
Kalbitor

JAN 16 2009

We are reviewing your biologics licensing application (BLA) submission dated September 23, 2008. We also acknowledge your submissions dated December 31, 2008, and January 13, 2009. We have identified the following possible issues. Please submit the requested information, by COB January 23, 2009, in order to facilitate our review of your BLA.

1. The analysis results submitted on Jan. 13, 2009, on the imputed data for EDEMA3 based on the rules specified in BLA submission do not match our analysis results. A summary of P values is given in the table below for EDEMA3. We would like to clarify if the efficacy variables we used for analysis of the imputed data are correct. We are interested in the efficacy endpoints (TOS and MSCS) at 4 hours post-dose.

	FDA results		Dyax results	
	TOS	MSCS	TOS	MSCS
Unimputed	0.045	0.041	0.045	0.041
Imputed for emerging symptom complexes	0.033	0.027	---	---
Imputed for emerging symptom complexes and medical intervention	0.017	0.016	0.037	0.044

The variables we used to do the analysis are:

TOS not imputed:

```
EFFVAR = 'TOS - NO IMPUTATIONS FOR EMERGING
SYMPTOM COMPLEXES OR MEDICAL INTERVENTION'
```

TOS imputed for emerging symptom:

```
EFFVAR='TOS - IMPUTATIONS FOR EMERGING SYMPTOM
COMPLEXES'
```

TOS imputed for emerging symptom complexes and medical intervention:

```
EFFVAR= 'TOS - IMPUTATIONS FOR EMERGING SYMPTOM
COMPLEXES AND MEDICAL INTERVENTION'
```

MSCS not imputed:

```
EFFVAR= 'MSCS 4 HOUR ANALYSIS - NO IMPUTATIONS FOR
EMERGING SYMPTOM COMPLEXES OR MEDICAL
INTERVENTION'
```

MSCS imputed for emerging symptom:

```
EFFVAR= 'MSCS 4 HOUR ANALYSIS - IMPUTATIONS FOR
EMERGING SYMPTOM COMPLEXES'
```

MSCS imputed for emerging symptom and medical intervention:

```
EFFVAR= 'MSCS 4 HOUR ANALYSIS - IMPUTATIONS FOR
EMERGING SYMPTOM COMPLEXES AND MEDICAL
INTERVENTION'
```

These variables are all from edema3db.xpt

The following are our SAS codes. If the variables listed above are the correct ones to use for analysis, please clarify why your results differ from our analysis. If you used different variables to do the analysis, please provide updated results based on these variables.

(b) (4)

(b) (4)

2. Provide analysis results on data imputation only for emerging symptom complexes in EDEMA3 with the rules specified in BLA submission.

3. Clarify how the unimputed data were defined when there were emerging symptoms and medical intervention. For example, clarify how the MSCS at 4 hour post-dose was defined when a patient had severe cutaneous symptom complexes at enrollment and a mild laryngeal symptom complex emerged at 2 hours post-dose and both symptom complexes remained unchanged 4 hour post-dose. Clarify if the emerging symptom complex was included or excluded in the calculation at both baseline and 4 hours post-dose. Please provide your calculation to the BLA. Please provide the same clarification on the definition of unimputed TOS.

4. The following comment pertains to your response to our comment 14.b.2 listed in our November 20, 2008, filing communication.

You did not commit to provide data supporting the use of normal human sodium citrated plasma rather than sodium citrated plasma from treatment naïve HAE patients to validate the assay for matrix effects. Please provide this data.

5. The following comment pertains to your response to our comment 14.c listed in our November 20, 2008, filing communication.

   The purpose of the parallelism study is to ascertain that the dilution series for the test article is appropriate for the standard curve. The curves in Fig 1 & 2 are biphasic with different slopes for drug concentrations ≤ 1.25 ng/mL and for drug concentrations ≥ 1.25 ng/mL. Re-plotting the data on a linear x-axis reveals that CVs at drug concentrations ≥ 1.25 ng/mL are clearly different from CVs at drug concentrations ≤ 1.25 ng/mL. Use of the MS Excel slope function is thus inappropriate for such data. Repeat the parallelism study using clinical samples and analyze the data using appropriate statistical methods.

6. The following comment pertains to your response to our comment 14.d listed in our November 20, 2008, filing communication.

   Please provide the CRO report you referenced in your response. It is unclear as to why you established a "cutoff" for this assay based on 4+SD. If the intent was to establish a LOD or LLOQ for measuring DX-88 in plasma, this is not reflected in the LLOQ reported in the BLA submission. Please clarify and modify your submission accordingly.

7. The following comment pertains to your response to our comment 15 listed in our November 20, 2008, filing communication.

   Please identify the location of the ECL data set obtained from 30 treatment naïve HAE patients. Reference to such data is made in Appendix E & F of TNJR07-081 but the cutoff values on page 103 of TNJR07-081 appear to show the difference in cutoff values between plate lots, not differences between NC serum and treatment naïve HAE patient serum cutoff values. Please clarify and provide the treatment naïve HAE patient data set if it exists.

8. The following comment pertains to your response to our comment 17.a.1 listed in our November 20, 2008, filing communication.

(b) (4)

(b) (4)

9. The following comment pertains to your response to our comment 17.b.1 listed in our November 20, 2008, filing communication.

   Please repeat the drug interference assay using a fina (b) (4)

10. The following comment pertains to your response to our comment 17.b.2 listed in our November 20, 2008, filing communication.

    (b) (4)

11. The following comment pertains to your response to our comment 17.b.3 listed in our November 20, 2008, filing communication.

    (b) (4)

12. The following comments pertain to all serum based assays.

    a. (b) (4)

13. The following comment pertains to the ELISA for measuring DX-88 in plasma (SOP QC-52-15)

> The short and long-term stability of all biological assay components needs to be established by you or the reagent manufacturer.

14. The following comments pertain to the ECL immunogenicity assay.

(b) (4)

15. The following comments pertain to the neutralizing anti-DX-88 antibody assay.

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

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: January 13, 2009

To: Nicole D'Auteuil	**From:** Colette Jackson
Company: Dyax	Division of Pulmonary and Allergy Products
Fax number:	**Fax number:** 301-796-9718
Phone number:	**Phone number:** 301-796-1230
Subject: BLA STN 125277 Comments	
Total no. of pages including cover: 2	

Comments:

Document to be mailed: YES xNO

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JAN 13 2009

BLA STN 125277
Kalbitor

We are reviewing your biologics licensing application (BLA) submission dated September 23, 2008. We have identified the following possible issues. Please submit the requested information, by COB January 21, 2009, in order to facilitate our review of your BLA.

On December 11, 2007, you submitted a protocol amendment to the Agency proposing to increase the sample size from 52 to 96 and to allow use of paper diaries in the EDEMA4 study. In our November 29, 2007, fax communication to you we requested that you perform additional assessments to ensure that sample size change had no impact on patient selection and study conduct. The assessments should include comparing characteristics of patients enrolled before and after sample size change and evaluation of treatment effect before and after sample size change.

In your BLA submission, we only found comparison on characteristics of patients enrolled before and after the change, but no analysis on the evaluation of treatment effect before and after the sample size change. Please provide your analysis on this issue and comment on the results.

Since the other change to the protocol with this amendment was to allow use of paper diaries, we also request the list of patients who used paper diaries and the list of patients who used electronic diaries in EDEMA4.

We need a clear understanding of how your data was handled in EDEMA3 and EDEMA4. Provide a detailed summary of your data handling, including but not limited to the following:

- Electronic diary development specifications and training procedures, including any training documents provided to the site
- Study-specific Site Operations Manual
- Data Handling Guidelines
- Clinical Data Monitoring Plan
- CROs involved in the data handling, including electronic diary vendor
- Delegation of responsibilities document
- Auditing Plan and individual site and CRO audit results, including name and affiliation of the auditor(s)
- Copy of paper diary (if used) and sample electronic diary

If there are any questions, please contact Colette Jackson, Regulatory Health Project Manager, at 301-796-1230.

Colette Jackson, Project Manager

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: January 7, 2009

To: Nicole D'Auteuil	**From:** Colette Jackson
Company: Dyax	Division of Pulmonary and Allergy Products
Fax number:	**Fax number:** 301-796-9718
Phone number:	**Phone number:** 301-796-1230
Subject: BLA STN 125277 Comments	
Total no. of pages including cover: (9)	

Comments:

Document to be mailed: YES xNO

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BLA STN 125277 JAN 7 2009
Kalbitor

We are reviewing your biologics licensing application (BLA) submission dated September 23, 2008. We also refer to your submission dated November 26, 2008. We have identified the following possible issues. Please submit the requested information, by COB January 12, 2009, in order to facilitate our review of your BLA.

1. Your submission dated November 26, 2008, included data clarification regarding the analysis dataset for EDEMA3 in response to our November 20, 2008, FDA communication. In your submission you state "*Based on the FDA comments, we also reviewed analysis datasets and specifications for the other individual EDEMA studies (EDEMA0, EDEMA1, EDEMA2, EDEMA3-RD, and EDEMA4). From this review, minor adjustments were made to the analysis dataset for EDEMA3-RD (edema3rd.xpt). We also made some minor modifications to the Analysis Dataset Specifications for all the EDEMA studies except for EDEMA1. A summary of the specific modifications is available upon request.*" Please explain in detail what specific modifications have been made to the datasets.

2. In the study report for DX-88/14(EDEMA3), the patient disposition summaries were given as below.

   For EDEMA3,

Table 3 Summary of Patient Disposition

	DX-88 (N=36)	Placebo (N=36)	Total (N=72)
	n (%)	n (%)	n (%)
Intent to Treat Population as Randomized[a]	36 (100.0)	36 (100.0)	72 (100.0)
Intent to Treat Population as Treated[b]	36 (100.0)	36 (100.0)	72 (100.0)
Per Protocol Population[c]	35 (97.2)	36 (100.0)	71 (98.6)
Safety Population[d]	36 (100.0)	36 (100.0)	72 (100.0)
Patients completing Study (double-blind)	35 (97.2)	36 (100.0)	71 (98.6)
Patients withdrawing from Study	1 (2.8)	0	1 (1.4)
Patients continuing onto Open-Label Part	21 (58.3)	27 (75.0)	48 (66.7)
If withdrawing from study, Primary Reason			
Adverse Event	0	0	0
Protocol Violation	0	0	0
Did not complete dosing	0	0	0
Did not complete 4 hour follow-up assessment	0	0	0
Lost to follow-up	1 (2.8)	0	1 (1.4)

Source: Summary Table 14.1.1

[a] Patients who received any amount of study drug and who completed their 4 hour follow-up assessment, analyzed with treatment assigned.

[b] Patients who received any amount of study drug and who completed their 4 hour follow-up assessment, analyzed with treatment actually received.

[c] Patients who received a completed dose of study drug and completed their 4 hour follow-up assessment with no major protocol violations.

[d] Patients who received any amount of study drug.

However, in the data set for EDEMA3 "edema3db.xpt", two patients in the DX-88 arm and one patient in the placebo arm have missing information on TOS and MSCS. The ITT population is defined as all patients who received any amount of study drug and who completed their 4 hour follow-up assessment. It is unclear as to why patients in the ITT population who completed their 4 hour follow-up assessment have TOS and MSCS data missing. Please clarify the discrepancies and provide an explanation on the missing data.

3. Please provide additional analyses using different imputation methods for patients who experienced emerging symptoms and medical intervention, if possible, based on the following new rules. Provide results of imputations for both EDEMA3 and EDEMA4.

   New imputation rules:

EMERGING SYMPTOM COMPLEXES

- *MSCS score*
  - *An emerging symptom complex is included in the baseline MSCS score calculation, with its baseline severity classified as peak severity.*
  - *An emerging symptom complex is included in the 4-hour and/or 24-hour calculations. If the emerging symptom complex is still present at 4 hours and/or 24 hours, its severity is used to calculate the MSCS score at these times. If the emerging symptom complex is not present at 4 hours and/or 24 hours, its severity is classified as "normal."*
- *TOS*
  - *An emerging symptom complex is weighted according to its severity assessment at its first appearing.*
  - *An emerging symptom complex that is still present at 4 hours and/or 24 hours is assigned a response assessment of "significant improvement." An emerging symptom complex that is not present at 4 hours and/or 24 hours is assigned a response assessment of "significant improvement"*

MEDICAL INTERVENTION

- *For the MSCS score, symptom complexes that are potentially affected are given a severity assessment of "normal" at 4 hours and/or 24 hours.*
- *For the TOS, symptom complexes that are potentially affected are given a response assessment of "significant improvement" and a severity assessment of "normal" at 4 hours and/or 24 hours.*
- *The overall response assessment is classified as "significant improvement" and a severity assessment of "normal" at 4 hours and/or 24 hours.*

4. The following comments pertain to the drug substance (ecallantide).

a. Provide the bioburden data for day 3 and day 5 for all product pools from the product pool storage studies.

b. (b) (4)

c. Provide a summary of the temperature data obtained during the drug substance shipping validation studies including the temperature range noted.

5. The following comments pertain to the drug product (Kalbitor™).

a. Data summaries of depyrogenation and sterilization validation studies should be provided in Module 3, Section P.3.5 of the submission. Please also refer to the 1994 FDA *Guidance for Industry – Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* for information that should be included in the application.

b. The submitted container-closure integrity study is not adequate for the following reasons:

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

Provide data summaries of an adequate microbial ingress study including a summary of the growth promotion results.

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

Commentary – Product-Wet Integrity Testing of Sterilizing Grade Filters – Points to Consider. PDA J. Pharm. Sci. Technol. 2008, 62 (5), 313-317.

f. Regarding depyrogenation of the 2 mL glass vials used for the product:

(1) Identify the (b) (4) used.

(2) Describe the load configurations.

(3) Provide the production and validation parameters.

(4) Provide data summaries of validation studies that demonstrate the effectiveness of the process to remove bacterial endotoxins. The validation data summaries should include the following:

(i) A description of the load configurations validated with rationale for their selection.

(ii) A description of the methods for (b) (4) endotoxin from the vials.

(iii) A description of the placement of thermocouples and (b) (4) vials.

(iv) A data summary of the temperature and endotoxin values obtained.

(v) The % recovery of endotoxin or positive control endotoxin value.

(5) Provide a description of the requalification program including the frequency and load configuration used.

(6) Provide a data summary of the most recent requalification results and how they compare to previous validation studies.

g. Regarding (b) (4) sterilization of stoppers:

(1) Identify the (b) (4) used.

(2) Describe the load configurations.

(3) Provide the production and validation parameters.

(4) Provide data summaries of validation studies (heat distribution and heat penetration) that demonstrate the effectiveness of the

sterilization process. The validation data summaries should include the following:

(i) A description of the load configurations (minimum, maximum, any variations) validated with rationale for their selection.

(ii) A description of the methods for inoculating and recovering biological indicators for (b) (4) studies.

(iii) A description of the placement of thermocouples and biological indicators:

(iv) A data summary of the temperature and biological indicator results obtained.

(v) The species, type, population and D-value of the biological indicator.

(5) Provide a description of the requalification program including the frequency and load configuration used (with rationale for the load selected).

(6) Provide a data summary of the most recent requalification results and how they compare to previous validation studies.

h. Regarding (b) (4) sterilization of equipment (b) (4)

(1) Identify the (b) (4) used or state if these equipment are sterilized in place.

(2) Describe the load configurations.

(3) Provide the production and validation parameters.

(4) Provide data summaries of validation studies (heat distribution and heat penetration) that demonstrate the effectiveness of the sterilization process. The validation data summaries should include the following:

(i) A description of the load configurations (minimum, maximum, any variations) validated with rationale for their selection.

(ii) A description of the methods for inoculating and recovering biological indicators for heat penetration studies.

(iii) A description of the placement of thermocouples and biological indicators.

(iv) A data summary of the temperature and biological indicator results obtained.

(v) The species, type, population and D-value of the biological indicator.

(5) Provide a description of the requalification program including the frequency and load configuration used (with rationale for the load selected).

(6) Provide a data summary of the most recent requalification results and how they compare to previous validation studies.

i. Regarding media fill simulations:

(1) Conflicting information is presented in Modules 2 and 3 regarding the vial size used to represent (b) (4) fills, the number of acceptable vials (b) (4) and fill duration (b) (4). Clarify and provide the rationale for each selection.

(2) Provide a data summary of the 3 most recent media fill runs including the following:

(i) The number of units filled the number of units inspected, the number of units discarded, and the number of units incubated.

(ii) A data summary of the growth promotion results for each run.

(iii) A summary of the interventions performed for each run.

(iv) A data summary of the environmental monitoring results for each run.

(v) State if media fills validate maximum holding times and provide the validated maximum holding time for each submitted media fill run.

j. Regarding environmental monitoring at Hollister-Stier:

(1) Provide the incubation conditions for each method.

(2) State if testing for yeasts and molds is performed.

(3) Clarify the difference between (b) (4)

k. Regarding bacterial endotoxins testing for product release:

(1) Provide the lysate sensitivity and test dilution used.

(2) State if samples are pooled for routine testing.

(3) Provide a data summary of enhancement/inhibition studies including the maximum valid dilution, lysate sensitivity and test dilution validated.

l. Regarding stability:

(1) The post-approval stability protocol does not include container-closure integrity testing at 24 months. It is not clear if this is intended or if it is an omission because testing is being conducted at 12 months and 36 months. Include the 24-month time point.

(2) Provide the protocol for the dye ingress container-closure integrity test to be used in stability testing.

(3) Provide the sensitivity of the dye ingress method and how it relates to the microbial ingress study submitted in the application.

If there are any questions, please contact Colette Jackson, Regulatory Health Project Manager, at 301-796-1230.

Colette Jackson, Project Manager

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: December 29, 2008

To: Nicole D'Auteuil	**From:** Colette Jackson
Company: Dyax	Division of Pulmonary and Allergy Products
Fax number:	**Fax number:** 301-796-9718
Phone number:	**Phone number:** 301-796-1230

Subject: BLA STN 125277 Clinical Pharmacology Comments

Total no. of pages including cover: 2

Comments:

Document to be mailed: YES xNO

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BLA STN 125277
Kalbitor

We are reviewing your biologics licensing application submission dated September 23, 2008. After reviewing the immunogenicity data in your submission, we have identified the following possible issues. Please submit the requested information, by COB January 9, 2009.

1. On page 137 of section 2.7.4 (Summary of clinical safety), we could not match the numbers in table 2.7.4.43 with the description in the preceding paragraph. Please re-check the data and explain how the numbers in this paragraph were obtained.

2. Section 3.6.1.2.1 (Numbers of Attacks to Seroconversion) summarizes the number of ecallantide-treated HAE attacks to seroconversion. Figure 2.7.4.1, Figure 2.7.4.2 and Figure 2.7.4.3 display the number of ecallantide-treated HAE attacks to seroconversion for anti-ecallantide (all classes) antibodies, anti-ecallantide IgE antibodies, and anti-P pastoris antibodies, respectively. However, the figures only summarized the immunogenicity in Analysis Population I. We request that you conduct the same analysis and draw the Kaplan-Meier plots in EDEMA3 and EDEMA4 (combined) patients only. We also request that you submit the dataset and SAS code used to generate the Kaplan-Meier plots for both Analysis Population I and for EDEMA3 and EDEMA4 (combined) patients. The data should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file.

If there are any questions, please contact Colette Jackson, Project Manager, at 301-796-1230.

Colette Jackson, Project Manager
12/29/2008

Drafted: December 29, 2008

Initialed: Barnes/ December 29, 2008
Xu, Yun/ December 29, 2008
Qiu/ December 29, 2008

Finalized: CCJ/ December 29, 2008

Filename: 125277 December 29 2008 clin pharm fax.doc

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: December 4, 2008

To: Nicole D'Auteuil	**From:** Colette Jackson
Company: Dyax	Division of Pulmonary and Allergy Products
Fax number:	**Fax number:** 301-796-9718
Phone number:	**Phone number:** 301-796-1230

Subject: BLA STN 125277 Clinical Pharmacology Comments

Total no. of pages including cover: 4

Comments:

Document to be mailed: YES xNO

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BLA STN 125277 DEC 4 2008
Kalbitor

We are reviewing your biologics licensing application submission dated September 23, 2008. Upon review of the bio-analytical reports for DX-88, we have the following requests in order to facilitate our review.

1. You have used three different assays to measure DX-88 concentration and submitted three method validation reports. For a full bio-analytical validation report, the following information are usually required (but not limited to): calibration curve range, defined LLOQ, linearity of the calibration curve, inter-assay and intra-assay precision/accuracy, recovery and stability data. However, in the submitted method validation reports, some of the above information is missing. Please provide this information. Also, provide a summary table to summarize these parameters for each individual study. If you have conducted any bridging studies to compare the performance among these different analytical assays, please submit the report.

2. DX-88 concentration has been measured in seven clinical studies, including DX88-1, 2, 4, 5, 6, 13, and 15. For each study with a drug concentration determination, a separate in-study bio-analytical report is required. In the report, the following information usually provided (but not limited to) are: calibration curve range, defined LLOQ, linearity of the calibration curve, QC (quality control) samples precision and accuracy. It appears you submitted the assay validation report instead of the in-study bio-analytical report for DX88-1 and DX88-13. You submitted the in-study bio-analytical report, for the remainder of the studies, but some of the above information was missing. For example, for the samples measured by TGA sciences, no QC information could be found. Therefore, we request you to examine and re-submit each in-study bio-analytical report with the parameters mentioned above. We also request you provide a summary table to summarize these parameters for each individual study.

3. We have identified three studies (DX-88/6, DX-88/2 and DX-88/4) that should be confirmed since the bioanalytical analysis were conducted by (b) (4) within the time frame of January 2000 and December 2004. We recommend that you repeat these studies, reanalyze the samples, or commit an independent scientific audit of the studies. You indicated that an external audit of (b) (4) (b) (4) was conducted to determine to what extent any analytical deviations would affect pharmacokinetic conclusions. Please submit the audit report.

4. In the Data Listing Dataset section of study report DX88/1 (Section 5.3.3.1.25.2.1), the concentration-time profile for individual subjects are missing. Please submit the dataset as a SAS transport files (*.xpt).

5. For study report "Population Pharmacokinetics and Pharmacodynamics of DX-88", please submit the following items:

   a. All datasets used for model development and validation. They should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

   b. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

   c. Please submit a combined dataset from Phase 2 and/or Phase 3 studies that would allow us to perform an exploratory exposure (Cmax, AUC, Cmin, and dose)-response (primary and secondary endpoints) analysis.

Please refer to the Guidance for Industry: Bioanalytical Method Validation (http://www.fda.gov/cder/guidance/4252fnl.pdf) for details. Please submit the requested above information, by COB December 11, 2008.

If there are any questions, please contact Colette Jackson, Project Manager, at 301-796-1230.

Colette Jackson, Project Manager

Drafted: December 2, 2008

Initialed: Barnes/ December 3, 2008
Xu, Yun/ December 3, 2008
Qiu/ December 3, 2008

Finalized: CCJ/ December 4, 2008

Filename: 125277 December 2008 clin pharm fax.doc

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125277/0

FILING COMMUNICATION

Dyax Corporation
300 Technology Square
Cambridge, MA 02139

NOV 20 2008

Attention: Nicole D'Auteuil
Senior Director, Regulatory Affairs

Dear Ms. D'Auteuil:

This letter is in regard to your biologics license application (BLA), dated September 23, 2008, received September 23, 2008, submitted under section 351 of the Public Health Service Act, KALBITOR™ (ecallantide) Injection.

We have completed an initial review of your application to determine its acceptability for filing. Under 21 CFR 601.2(a), we filed your application today. The review classification for this application is Priority. Therefore, the user fee goal date is March 23, 2008. 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.

During our filing review of your application, we identified the following potential review issue:

> Ecallantide is likely to be used in settings outside the usual healthcare delivery environment, such as self-administration by patients. The clinical trials included in the development program did not specifically evaluate the safety or efficacy of self-administration by patients. Address the issue of self administration of ecallantide, including information to support the safety and efficacy of self-administration and the risk of hypersensitivity reactions and other adverse events in this setting.

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 this issue 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.

We also request that you submit the following information:

1. Provide a safety update of Study DX-88/19 (EDEMA4 open-label extension study) by December 22, 2008.

2. The following comments pertain to the Highlights section of the product label.

   a. Do not use the "TM" or "R" symbols after the drug names in Highlights or Table of Contents. These symbols can be used once upon the first use in the Full Prescribing Information section.

   b. Please note that for biologic products, the dosage form and route of administration must be on the next line (i.e., underneath the proper name) since the proper name does not include the drug's dosage form or route of administration. See 21CFR 600.3(k) and Section 351 of the Public Health Service Act.

3. Please describe in detail, the characterization studies performed for the evaluation of the cell substrate used for production of Kalbitor (e.g., Master Cell Bank, Working Cell Bank and End of Production Cells). Provide the results of these tests especially for the End of Production Cells including those used for purity as described in ICH Q5D *"Derivation And Characterization Of Cell Substrates Used For Production Of Biotechnological/ Biological Products"*, section 3.3.2 (i.e., absence of bacterial and fungal contamination). Please note that a purity assessment should include a test for the presence of [redacted] (b) (4) Please submit the results of this characterization.

4. Provide the results from your drug product Shipping Validation studies.

5. Clarify if you intend to submit a comparability protocol for future manufacturing changes. If so, submit the protocol to the BLA.

6. Provide a full description of your assay for the equilibrium inhibition constant (K_i) and the validation or qualification studies to show that the assay is suitable for its intended use. Additionally, please address the high variability seen with the results obtained with the K_i assay; *e.g.*, the results for the characterization of purified [redacted] (b) (4) (Table 3.2.S.3.2.1) show standard deviations as high as 83%.

7. As part of product characterization, you have suggested that aggregated forms of ecallantide are generated through the formation of covalent intermolecular disulfide bonds. However, you show that the [redacted] (b) (4) (b) (4)

8. Provide the data to support the [redacted] (b) (4) range f[redacted] (b) (4) for the [redacted] (b) (4) step [redacted] (b) (4)). Also provide the data to justify the statement that [redacted] (b) (4) does not affect overall yields.

[redacted] 2 pp withheld immediately after this page as (b)(4) CCI/TS

(b) (4) and a (b) (4). Describe the generation and characterization of this surrogate PC.

b. Confirm your assay sensitivity using immunoaffinity purified antigen specific human IgG from DX-88 immune HAE patient serum.

17. The following comments pertain to the neutralizing anti-DX-88 antibody assay.

a. The following comments pertain to data analysis.

(1) Most of the data is presented as % neutralization of enzymatic activity. Present representative data for all the plots and tables without normalization.

(2) Explain why the limit for the NC/Blank ratio < (b) (4)

b. The following comments pertain to the confirmatory drug inhibition assay.

(1) (b) (4)

(2) (b) (4)

(3) Provide data supporting the use of normal human serum rather than treatment naïve HAE patient serum to determine the assay cut-point.

18. The following comment pertains to the IgE anti-DX-88 antibody ELISA ((b) 334-1106).

(b) (4)

signal. Please provide the following information:

a. (b) (4)

b.

c.

19. The following comment pertains to IgE anti-P.pastoris antibody ELISA (b) 335-1106).

(b) (4)

Please respond 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.

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 waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application for pediatric patients.

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 Colette Jackson, Regulatory Health Project Manager, at (301) 796-1230.

Sincerely,

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: November 20, 2008

To: Nicole D'Auteuil	**From:** Colette Jackson
Company: Dyax	Division of Pulmonary and Allergy Products
Fax number:	**Fax number:** 301-796-9718
Phone number:	**Phone number:** 301-796-1230
Subject: BLA STN Statistical Comments	
Total no. of pages including cover: 3	

Comments:

Document to be mailed: YES xNO

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BLA STN 125277
Kalbitor

NOV 20 2008

We are reviewing your biologics licensing application submissions dated September 23, and October 28, 2008 and we have the following request in order to facilitate our review.

Please clarify the analysis dataset for EDEMA3 (edema3db.xpt). The following four TOS were included in the dataset.

1. TOS - IMPUTATIONS FOR EMERGING SYMPTOM COMPLEXES - SUAC FAILURE (time point: 4 hours and 24 hours)

2. TOS - IMPUTATIONS FOR EMERGING SYMPTOM COMPLEXES AND MEDICAL INTERVENTION - SUAC FAILURE (time point: 4 hours and 24 hours)

3. TOS - IMPUTATIONS FOR EMERGING SYMPTOM COMPLEXES - ROBUST (time point: 4 hours)

4. TOS - NO IMPUTATIONS FOR EMERGING SYMPTOM COMPLEXES OR MEDICAL INTERVENTION - SUAC FAILURE (time point: 4 hours and 24 hours)

In the definition file, the first TOS was reported to include measures at both 4 hours post-dosing and 24 hours post-dosing, but in the data, all of them are labeled for 4 hours post-dosing. Please clarify if this is the result of a program error. If it is a program error, please provide an updated dataset with the corrected information on time point.

If there are any questions, please contact Colette Jackson, Project Manager, at 301-796-1230.

Colette Jackson, Project Manager

NOV 20 2008

Drafted: November 18, 2008

Initialed: Barnes/November 18, 2008
Liu/November 19, 2008
Li/ November 20, 2008

Finalized: CCJ/ November 20, 2008

Filename: 125277 November 2008 stats fax

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

BLA ACKNOWLEDGEMENT

Our STN: BL 125277/0

Dyax Corporation
300 Technology Square
Cambridge, MA 02139

OCT 29 2008

Attention: Nicole D'Auteuil
Senior Director, Regulatory Affairs

Dear Ms. D'Auteuil:

We have received your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for the following:

Name of Biological Product: KALBITOR (ecallantide) Injection

Date of Application: September 23, 2008

Date of Receipt: September 23, 2008

Our Submission Tracking Number (STN): BL 125277/0

Proposed Use: Treatment of Hereditary Angioedema

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. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission.

If you have any questions, call me at (301) 796-1230.

Sincerely,

Colette Jackson
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

MEMORANDUM OF TELECON

DATE: November 12, 2008

APPLICATION NUMBER: BLA STN 125277

NOV 26 2008

BETWEEN:

Name: Nicole D'Auteuil, Senior Director, Regulatory Affairs
Peggy Berry, Regulatory Affairs
Bill Pullman, M.D., Ph.D., Chief Development Officer

Phone: 1-888-583-1346

Representing: Dyax Pharmaceuticals

AND

Name: Badrul A. Chowdhury, M.D., Ph.D., Division Director
Sandy Barnes, Chief Project Management Staff
Sally Seymour, M.D., Clinical Team Leader
Susan Limb, M.D., Clinical Reviewer
Colette Jackson, Project Manager
Division of Pulmonary and Allergy Products

SUBJECT: Status of BLA 125277

Dyax Pharmaceuticals submitted their BLA on September 23, 2008, seeking an indication for hereditary angioedema. This application has been granted orphan drug designation and fast track status. Dr. Chowdhury opened the discussion, noting that the Agency would like to provide some preliminary comments on the status of BLA STN 125277. Dr. Chowdhury also noted that no official regulatory decisions have been made. Dr. Chowdhury informed Dyax that the acceptability for filing the application is under consideration. The Agency acknowledged the importance of the drug for a patient population for which there are no treatment options. The Agency also acknowledged Dyax's request for a priority review of the application. If the Agency grants the request for a priority review, this application will have a 6-month review clock and a PDUFA date of March 23, 2009. Dr. Chowdhury noted that the dates Dyax offered the Agency for inspection of the facility were February 23-27, 2009, 4 weeks from the PDUFA date. The timeline for the inspection conflicts with the compressed GRMP timelines for the application. Dr. Chowdhury referred Dyax to 21 CFR 600.21, 601.2(d) and 601.20(b) and noted that the company must be ready for inspection ***at the time of filing of the BLA***.

Dyax stated that the facility is ready for inspection. Dyax is using a contract facility and is limited as to when a manufacturing run can be conducted, but noted that they are willing to work with the contract facility and the Agency to agree on a mutually acceptable date for inspection that will allow for adherence to GRMP timelines. Dyax stated that they would like to have a

priority review for the application, and assured the Agency that there is flexibility in the dates for inspection of the contract facility. Dr. Chowdhury stated that this information will be discussed with the Division of Manufacturing and Product Quality in the Office of Compliance, and suggested that Dyax also contact the Office of Compliance. Dr. Chowdhury did inform Dyax that if the February 23, 2009, timeframe is the only acceptable date, then an internal decision will need to ensue regarding the possibility of not filing the application. Dr. Chowdhury also noted that since this is a new molecular entity, an Advisory Committee meeting is tentatively scheduled for this application.

Dyax stated they will contact the Office of Compliance and Dr. Chowdhury stated he will contact them as well.

Colette Jackson
Regulatory Health Project Manager

NOV 26 2008

Drafted: CCJ/ November 17, 2008
Initialed:
Seymour/ November 17, 2008
Limb/ November 17, 2008
Barnes/ November 26, 2008
Chowdhury/ November 26, 2008

Finalized: CCJ/ November 26, 2008

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type:	Type B
Meeting Category:	PreBLA
Meeting Date and Time:	October 30, 2007
Meeting Location:	Food and Drug Administration Center for Drug Evaluation and Research Division of Pulmonary and Allergy Products 10903 New Hampshire Avenue Building 22, Conference Room 1417 Silver Spring, Maryland 20993
Application Number:	BB IND 10426
Product Name:	Ecallantide
Received Briefing Package	October 2, 2007
Sponsor Name:	Dyax Corporation
Meeting Requestor:	Aurelie Grienenberger, PhD Director, Regulatory Affairs
Meeting Chair:	Badrul A. Chowdhury, MD, PhD Division Director
Meeting Recorder:	Akilah Green, MS, RN Senior Regulatory Management Officer

1.0 BACKGROUND

Dyax submitted a Type B meeting request dated August 1, 2007, to discuss their proposed BLA submission format and planned deliverables in electronic Common Technical Document format. Dyax's briefing package was dated October 1, 2007. Upon review of the briefing package, the Division responded to Dyax's questions via fax on October 26, 2007. The content of that fax is printed below. Any discussion that took place at the meeting is captured directly under the relevant original response including any changes in our original position. Novartis' questions are in ***bold italics***; FDA's response is in *italics*; discussion is in normal font.

2.0 DISCUSSION

CMC

2.1 QUESTION 1

The chemistry, manufacturing and control information will be summarized in the appropriate CTD sections in Module 3. In addition, Dyax proposes to include the following technical reports to the specific Module 3 sections:

- ***Process consistency reports for drug substance and drug product included in Sections 3.2.S.2.5 and 3.2.P.3.5***
- ***Executed batch record for one consistency batch of drug substance and for one consistency batch of drug product in 3.2.R.1.***
- ***Method validation reports, as required in 21 CFR 314.50, included in Sections 3.2.S.4.3 and 3.2.P.5.3.***

Does the FDA agree with this proposal?

<u>FDA Response to Question 1:</u>

Yes, we agree with your proposal, however we have the following comments:

1. In the process consistency studies, you will need to demonstrate that the commercial manufacturing process is under control and meets cGMP requirements. You will need to substantiate the critical process controls and their limits for critical process manufacturing steps. To support your limits for critical process manufacturing steps, you may include data from small scale manufacturing processes provided that the small scale manufacturing process is representative of the large scale commercial manufacturing process.

2. You will need to provide characterization data on the primary, secondary and higher-order structures of DX-88, and post-translational modifications. You should perform forced degradation and stress studies as part of your product characterization such as oxidative stress, heat and humidity, shaking, pH, etc. The samples generated from the stress studies should be used in your analytical assays to determine which assays can detect product degradation (i.e., are stability-indicating). In addition, you should determine if the degradation products have or contribute to the bioactivity of DX-88.

3. Your specifications for the drug substance (DS) and drug product (DP) will need to be justified based on your manufacturing history and the characteristics of the lots used in clinical trial used to show safety and efficacy. We recommend that you use statistical analysis to set your specifications, e.g., tolerance intervals.

4. (b) (4)

Discussion:

The FDA stated that Dyax should control for increases and decreases in the (b) (4) species. Dyax can submit an amendment with questions.

5. In addition to the shelf-life studies, you will need to demonstrate that your assays are stability-indicating using data derived from stress and long-term stability studies and the forced degradation studies. Provide shipping validation studies, photostability studies and leachable and extractables data for the container closure systems used for the DS and DP. Provide stability protocols for the annual commercial testing of DS and DP lots.

Discussion:

The FDA told Dyax that their BLA submission needs to be complete at the time of submission. Both DS and DP executed shipping protocols should be included in the BLA. The shipping validation is typically performed in two parts; a mock shipping study where samples of diluent are shipped in the appropriate shipping container with

temperature indicators and an agitation study. These studies are best done in the real world setting; however, it is possible to perform these studies in the laboratory.

6. [redacted] (b) (4)

Discussion:

The FDA noted that we are concerned about Dyax's multiple incidences of failing. Dyax indicated that they completed their investigation of the problem and will include it in the BLA.

7. You will need to provide full characterization data for your DS and DP reference standards. We recommend that you provide a comparability protocol for the qualification of future reference standards. As part of the qualification, perform all of your standard release assays as well as additional characterization tests. In addition, provide comparability data for the old and the new reference standards.

8. [redacted] (b) (4)

Discussion:

Dyax stated that they will submit their additional testing in an IND amendment.

9. Please clarify if you have received approval for the Ecallantide name from USAN.

Discussion:

Dyax confirmed that they have approval, which they will file in the BLA.

2.2 QUESTION 2

Assuming that the calculation for the estimated concentration of ecallantide at the point of entry into the aquatic environment be below 1 part per billion, Dyax intends to request a categorical exclusion for environmental assessment as described in 21 CFR 25.31(b). Does the FDA have any comments on the proposed plan?

FDA Response to Question 2:

The proposed plan is acceptable.

NONCLINICAL

2.3 QUESTION 1

Does the FDA have any comments or requests concerning the nonclinical documentation to be presented in Module 4 or Module 2, as described in Section 5, Table 22 and Table 24?

FDA Response to Question 1:

We do not have any comments at this time.

CLINICAL

2.4 QUESTION 1

Introductory Comment:

We note that your planned BLA submission format does not include efficacy data from EDEMA4, and EDEMA4 safety data will only be included in the 4-month safety update. As communicated to you in our fax, dated July 11, 2007, we have concerns regarding the viability of this approach. We recommend you refer to the Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products regarding the evidence necessary to establish the effectiveness of a drug or biological product. This guidance describes the situations in which a single study may support approval e.g. a multicenter study of excellent design providing highly reliable and statistically strong evidence of an important

clinical benefit. Based upon the information you provided, EDEMA3 does not fulfill this expectation. We believe that the results from another adequate and well-controlled study (such as EDEMA4) are necessary to assess the safety and efficacy of your drug product. Submission of an application which does not contain information needed for approval is contrary to the operating principles outlined in the Guidance for Review Staff and Industry: Good Review and Management Principles and Practices for PDUFA Products. Furthermore, while we expect a safety update during the review period, keep in mind that all data needed to support the efficacy and safety of your drug product for approval should be included in the original BLA submission.

Discussion:

Dyax stated that they have substantial evidence of safety and efficacy data up to and including EDEMA 3. Dyax began the SPA with EDEMA 4 when EDEMA 3 was still ongoing. They feel EDEMA 4 is worthwhile; however, the results of EDEMA 3 are compelling with the endpoints set forward. The FDA noted that the determination of whether we will refuse to file the submission will be made 60 days after receipt of the submission; we can not prejudge the data. However, based on previous discussions and preliminary review of the results, we do not think the data necessary for approval will be present in the findings from EDEMA3. The GRMP guidance expects first cycle approval. If Dyax's submission is lacking a pivotal study, we may refuse to file it. Given Dyax's recent insistence upon an SPA agreement for EDEMA4 as a pivotal study, we were surprised that Dyax feels that EDEMA3 alone would provide sufficient support for a BLA. Dyax responded that the Agency's comments would be taken into consideration.

As our efficacy dataset for this rare condition is relatively small, Dyax proposes to locate all efficacy summary information and integrated discussion of efficacy in Module 2, Section 2.7.3. Is this approach acceptable?

FDA Response to Question 1:

Yes, this approach is acceptable.

2.5 QUESTION 2

During development, efficacy data was collected using different endpoints, doses, and routes of administration in Module 2. Efficacy data will be discussed in an integrated manner without data pooling. Dyax plans specifically to present efficacy analyses: on first dose versus placebo, repeated doses over time for treatment of subsequent attacks, and positive immunological response to ecallantide. Does the FDA request that we include any other specific efficacy analysis?

FDA Response to Question 2:

Since subjects were permitted to participate in multiple sequential protocols, the efficacy section of your BLA submission should clearly identify these patients and

account for them in the analyses. In addition, if possible, identify which patients have Type I versus Type II HAE. As discussed previously (Fax dated September 24, 2007), we expect the primary analyses to be presented as pre-specified in the respective protocols. Imputations for missing data may be submitted as additional sensitivity analyses.

Discussion:

Dyax asked the FDA to clarify their expectations on the presentation of the data sets. Dyax plans to discuss the data in a side by side manner. The FDA stated that Dyax needs to find a way to identify clearly the patients who participated in multiple studies. Double-counting of these patients may affect the interpretation of safety and efficacy results. We do not have a specific type of analysis in mind, but Dyax may want to do additional analysis to address how they affect efficacy. With regard to data imputation, Dyax indicated that they pre-specified doing imputations with EDEMA 3. However, with EDEMA 4 they will file the statistical analysis plan in advance of executing without imputation.

2.6 QUESTION 3

In DX-88/14 (EDEMA3) study, 2 patients who were treated at the same study center on the same day and at approximately the same time were given the treatment assigned to the other patient. The treatment error was noted real-time during the study conduct. Therefore, the patients will be analyzed according to the treatment they received. Dyax believes this ITT patient population best reflects the true efficacy of ecallantide because it represents the actual treatment that each patient received. Dyax therefore intends to present the primary efficacy analysis and each secondary efficacy analyses using this population. Does the FDA agree?

FDA Response to Question 3:

No, we do not agree. The efficacy analysis should use the original ITT population. Analysis based on a modified ITT population may be included as an additional analysis. Given the small numbers of patients in the study, both analyses will be taken into account in our review.

2.7 QUESTION 4

As the ISS is expected to be small and in accordance with FDA guidance for integrated summaries[1], Example 2, Dyax proposed that the full ISS is placed in Module 5 (section 5.3.5.3) and the text portion of the ISS is repeated in Module 2

[1] ***FDA Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document, June 2007***

(section 2.7.4) as the Summary of Clinical Safety. Is this approach acceptable for the FDA?

FDA Response to Question 4:

Yes, this approach is acceptable.

2.8 QUESTION 5

Are any additional safety analyses required for the BLA submission, in addition to the planned analyses described in Section 6.4.5?

FDA Response to Question 5:

For the proposed indication, we are most interested in the safety data in the HAE population. You propose pooling populations (HAE/CTS/HV and HAE/CTS) for the primary analysis of the safety data. While you may choose to pool the safety data from these populations, we request that all the analyses performed on the primary pooled populations also be performed on the HAE subpopulation. We have the following additional requests:

1. Since subjects were permitted to participate in multiple sequential protocols, the safety section of your BLA submission should clearly identify these patients and account for them in the ISS.

2. For laboratory, vital sign, and ECG data, identify patients with significant changes (outliers) using shift tables.

3. In addition to common adverse events (AEs), include an analysis of less common or rare adverse events.

4. Include discussion of AEs based upon gender, race, and age subpopulations as well as special populations, such as patients with renal or hepatic impairment.

5. Include analyses of AEs based upon exposure.

6. Include a discussion on the immunogenicity of ecallantide and correlation with AEs.

2.9 QUESTION 6

Throughout the clinical program for ecallantide, pediatric patients with HAE between the ages of 10 and 16 years of age have been included in the study populations. In our clinical program, pediatric patients therefore represent approximately 11% of treated HAE patients and their attacks represent approximately 20% of all treated attacks. Literature indicates that children under 10 are infrequently diagnosed and/or symptomatic with HAE. Based on the orphan status of ecallantide in the treatment of HAE, this application qualifies for a pediatric exemption as described in 21 CFR 314.55(d) and Dyax will not conduct additional pediatric investigations. Does the FDA concur?

FDA Response to Question 6:

We request that your BLA address pediatric use of ecallantide. Your safety and efficacy analyses should include subgroup analyses for the pediatric subpopulation.

Discussion:

Dyax intends to submit subgroup analysis for the pediatric patients and asked for further clarification on FDA's response to Question 6. FDA stated that Dyax should provide information on the use of ecallantide in the pediatric population and any future plans for studies in younger age groups. The strength of the findings and the ages for which data are available will determine the lower age limit for product labeling purposes. The FDA does not have pre-specified age ranges for performing subgroup analysis.

2.10 QUESTION 7 a & b

Patient Reported Outcome (PRO) Validation Documentation will be provided as follows:

Table 2 PRO Validation Documentation Included in the BLA

Report Title and Number	Report Content and Scope	Location in the CTD
Evidence Dossier for the Use of the TOS and MSCS in DX-88 Treatment for Hereditary Angioedema (UBC A2-4274-001)	*Summary report of the development and validation of the PRO MSCS and TOS*	**Section 5.3.5.3** Reports of Analyses of Data from More than One Study
Establishing the Content Validity of an Electronic Diary Form of the Treatment Outcome	*Cognitive debriefing report to establish the content validity of the*	**Section 5.3.5.4** Other Study Reports

Table 2 PRO Validation Documentation Included in the BLA

Report Title and Number	Report Content and Scope	Location in the CTD
Score and Mean Symptom Complex Score for Angioedema Via Cognitive Debriefing Interviews (UBC A2-4274)	*PRO TOS and MSCS*	
Reliability and Validity of the TOS and MSCS in Patients with Hereditary Angioedema (UBC A2-6425)	*Statistical analysis of EDEMA3 study to establish the reliability and validity of the PRO TOS and MSCS*	**Section 5.3.5.4** Other Study Reports
DX-88/5 EDEMA2 Study Report (Dyax DX-88/5)	*EDEMA2 Clinical Study Report includes initial validation activities for PRO MSCS and TOS*	**Section 5.3.5.2** Study Reports Of Uncontrolled Clinical Studies

7a/ Does the FDA agree with the proposed location in the CTD of the PRO validation documentation?

7b/ Would FDA also prefer a separate submission of the PRO validation documentation for SEALD review?

<u>FDA Response to Questions 7 a & b:</u>

The proposed location in the CTD of the PRO validation documentation is acceptable. Submit a separate copy of the PRO validation documentation for SEALD review. In addition, the SEALD team has provided a template of documentation that should be included in your BLA:

A. Targeted Claims

1. List all targeted treatment benefit claims for the medical product;

2. Identify specific claims to be supported by PRO instruments and endpoints;

3. Link each targeted PRO claim to a concept measured by PRO instrument(s).

B. Model of Hypothesized Relationships among Endpoints (Endpoint Model)

1. List all measures (PRO and non-PRO) that were used as study endpoints in the clinical trial(s) to support claims. (This may include physiologic\lab\physical, clinician-reported or patient-reported measures.);

2. Describe hypothesized relationships among these measures.

C. PRO Conceptual Framework

1. For each PRO instrument that is comprised of more than a single item, provide a diagram of concepts measured by each item, domain, and overall score.

2. Provide documentation described below to confirm the conceptual framework.

D. Instrument Development, Item Generations, and Content Validity

1. Chronology of all item development activities;

2. Summary of literature reviews;

3. Protocols for qualitative interviews and focus groups, cognitive debriefing interviews and any other research used to identify concepts, generate items, or revise an existing instrument;

4. Item tracking table that list the source of each item in the final instrument;

5. Development of response options and scoring;

6. Size, characteristics, location, and transcript of each focus group;

7. Documentation that saturation was achieved (i.e. no new information was obtained from additional qualitative interviews or focus groups);

8. Cognitive debriefing transcripts;

9. Versions of the instrument at various milestones of development (including the final version that was used in your clinical trial);

10. A summary statement of qualitative research in support of content validity of the PRO instrument, i.e., how does the qualitative research listed above support the conclusion that the PRO instrument measures the concept(s) that it purports to measure and that are reflected in the proposed claims.

E. Assessment of PRO Properties

1. Protocols for PRO instrument development (design, methods, analysis plan);

2. Documentation of psychometric testing for each domain or summary score proposed as support for claims;

   a. Confirmation of conceptual framework (concepts, domains, scores);

   b. Reliability

      i. Cronbach's alpha

      ii. Test-retest

   c. Construct validity

      i. Convergent

      ii. Discriminant

   d. Ability to detect change

3. Descriptive and statistical analysis findings from each study;

4. Estimate of patient burden;

5. Instrument user manual that includes:

   a. Procedures for PRO administration in its final format;

   b. Scoring;

   c. Final version of instrument;

F. Modifications of Existing Instruments

1. For language translations and cultural adaptation processes, include:

   a. Description of the expertise of the translators;

   b. Description of procedures used (forward, back, reconciliation, harmonization);

   c. Description of patient testing;

   d. Results of translation/adaptation including clear description of all translation issues and how they were resolved.

2. For content, wording, format, or mode of administration changes, describe results from studies conducted to evaluate modification, or rationale for not conducting studies.

3. For use in a new indication or new population, document instrument development and assessment of measurement properties as described above.

G. Protocol-related documentation: In addition to usual protocol concerns

1. The final version of the instrument planned used in the clinical trials;

2. Instrument administration procedures, training and instructions for patients and study personnel;

3. Data collection, data storage, and data handling/transmission procedures;

4. Statistical analysis plan

   a. Responder definition, if applicable;

   b. How between-group differences were interpreted (e.g., cumulative distribution function);

   c. Documentation of how the PRO instrument measurement properties within the clinical trial were confirmed;

   d. What were your plans to avoid missing data at both the instrument and patient levels.

H. Bibliography

1. Provide copies of all relevant published and unpublished documents.

Discussion:

FDA clarified that separate paper documentation for the SEALD team will not be necessary if the BLA is filed electronically.

2.11 QUESTION 8

Does the FDA have any comments or requests concerning the format of Module 5 deliverables, as described in Table 25?

FDA Response to Question 8:

No, we do not have any other comments at this time.

Clinical Pharmacology Comment:

Include raw PK data and PK parameter datasets for all PK studies. In addition, the pooled datasets and control files for population PK evaluation should be included.

Discussion:

FDA clarified that PK datasets of individual studies and pooled datasets for population PK analysis should be reported as SAS transport files.

REGULATORY

2.13 QUESTION 1

At the time of BLA submission, Dyax intends to request priority review. For planning purposes, if priority review is granted, would the Division prefer submission of the required safety update at the day 120 timepoint or at some other time?

FDA Response to Question 1:

We remind you that all data needed to support the efficacy and safety of your product should be submitted with the complete application. A safety update should be submitted at 4 months.

2.14 QUESTION 2

As communicated in August 2006, because ecallantide for the treatment of acute attacks of HAE is designated as a Fast Track development program, Dyax proposes to submit the BLA in a rolling fashion. The specific plan for submission is presented in Table 4. Dyax understands that the review clock (whether priority or standard) will not begin until the BLA submission is complete. Does the FDA agree with the proposed submission plan as outlined in Table 3?

Table 3. Proposed Rolling Submission Plan

	Rolling CMC Submission	**Rolling NC Submission**	**Full BLA Submission**
Submission Date	December 2007	February 2008	Within 6 months of CMC rolling submission (By June 2008)
Submission Format	eCTD	eCTD	eCTD

Table 3. Proposed Rolling Submission Plan

	sequence 0000	sequence 0001	sequence 0002
Content	**Module 1:** Cover Letter Form FDA 356h **Module 2:** 2.2 Introduction 2.3 Quality Overall Summary **Full Module 3**	**Module 1:** Cover Letter Form FDA 356h **Module 2:** update to 2.2 Introduction 2.4 and 2.6 Nonclinical Overview and Summaries **Full Module 4**	**Full Module 1** **Full Module 2** with updates to Sections 2.2 Introduction and 2.3 Quality Overall Summary based on updates in Module 3 **Module 3** Updates only on Drug Substance and Drug Product Stability (3.2.S.7 and 3.2.P.8) **Full Module 5**

FDA Response to Question 2:

While you may submit portions of your application as outlined, we cannot commit to reviewing the application until the BLA submission is complete. We remind you that Fast Track designation does not necessarily lead to Priority Review. A determination of Priority versus Standard review will be made at the time of BLA submission.

2.15 QUESTION 3

The BLA will be submitted in eCTD format. File sizes will be 100MB or smaller and any deviation will be noted in the cover letter. Is this acceptable?

FDA Response to Question 3:

The proposed plan is acceptable, although you should note that 100MB is the upper limit file size. Smaller file sizes, when possible, will facilitate handling.

2.16 QUESTION 4

Does the FDA have any other comments or requests to ensure the application is in the appropriate format and has the summary documents required for review?

Additional information regarding the BLA submission format is provided in Section 7 of this package

FDA Response to Question 4:

We do not have any additional comments regarding the BLA submission format at this time.

OUTSTANDING BUSINESS

2.16 QUESTION 1

Dyax submitted a proposal for additional QT/QTc assessment (Serial 164, dated 24 August 2007) for FDA review with questions. At the time of submission of this briefing document, the responses are pending. In the event that the FDA has not responded prior to the pre-BLA meeting, we would like to incorporate these questions into the meeting.

FDA Response to Question 1:

Your BLA submission should include a completed assessment of QT prolongation risk. In lieu of a thorough QT study, ECG monitoring as proposed in the EDEMA4 protocol (ECG at screening, pre-dose, 2 hours-post-dose, 4 hours-post-dose, and Follow-up Visit 1), interpreted by a central reader, is an acceptable alternative.

Discussion:

Dyax stated that comparable ECG monitoring minus the 4 hour post-dose timepoint was performed in EDEMA3 and questioned whether this data would satisfy the requirement for QT assessment. The FDA replied that it was up Dyax to determine if the appropriate QT assessment had been made in their clinical program, noting that it seems unlikely that a rigorous QT assessment could have been accomplished without advance planning. For example, the Clinical Pharmacology review team pointed out that the 4-hour post-dose timepoint was important based on the Cmax of ecallantide. However, if Dyax believes that EDEMA3 ECG monitoring included the appropriate timepoints and interpretation by a central reader, the ECG results should be included in the BLA submission.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues discussed at the meeting that required further discussion.

4.0 ACTION ITEMS

There were no action items identified during the meeting.

5.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts used during the discussion at the meeting.

Meeting Attendees:

FDA Attendees

Office of Drug Evaluation II, Division of Pulmonary and Allergy Products

Badrul A. Chowdhury, MD, PhD, Director

Sally Seymour, MD, Clinical Team Leader

Susan Limb, MD, Clinical Reviewer

C. Joe Sun, PhD, Pharmacology/Toxicology Supervisor

Jean Wu, PhD, Pharmacology/Toxicology Reviewer

Akilah Green, MS, RN, Senior Regulatory Management Officer

Office of

Office of Biostatistics, Division of Biometrics II

Qian Li, Ph.D., Acting Biostatistics Team Leader, Office of Biostatistics,

Office of Clinical Pharmacology Division of Clinical Pharmacology 2

Wei Qiu, Ph.D., Acting Clinical Pharmacology Team Leader

Office of Biotechnology Products, Division of Therapeutic Proteins

Susan Kirshner, Ph.D., Quality Review Team Leader

Kathy Lee, Ph.D., Quality Reviewer

Dyax Corporation Attendees

Khandan Baradaran, PhD, Senior Manager, Regulatory Affairs

Peggy Berry, Senior Vice President, Quality and Regulatory Affairs

Marc Blaustein, Senior Vice President, Manufacturing, Process and Commercial Operations

Matthew Gollwitzer, Sr Specialist, Regulatory Affairs

Aurelie Grienenberger, PhD, Director, Regulatory Affairs

Patrick Horn, MD, PhD, Senior Medical Director

Bill Pullman, MD, PhD, Executive Vice President Chief Development Officer

Christopher TenHoor, PharmD, PhD, Vice President, Pharmacology and Preclinical Development

Barry Turnbull, PhD, Vice President, Biometrics, BattelleCRO

Fayelle Whelihan, PhD, Senior Vice President, Program Management

Drafted by:	Green/November 19, 2007
Initialed:	Chowdhury/November 20, and 29, 2007
	Limb/November 20, 2007
	Qui/November 27, 2007
	Lee/November 28, 2007
Finalized:	Green/November 29, 2007

Linked Applications	Sponsor Name	Drug Name
IND 10426	DYAX CORP	Kallikrein Plasma Inhibitor (recombinant, Pichia pastoris, Avecia Biotechnology)

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/s/

AKILAH K GREEN
11/29/2007

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

Memorandum of Facsimile Correspondence

Date:	November 29, 2007
To:	Aurelie Grienenberger Associate Director, Regulatory Affairs
Company:	DYAX Corp
Fax:	(617) 225-2501
Phone:	(617) 250-5762
From:	Akilah Green, RN, MS Senior Regulatory Management Officer Division of Pulmonary and Allergy Products
Fax:	(301) 796-9718
Phone:	(301) 796-1219
Subject:	BB IND 10426; Meeting minutes for October 30, 2007, meeting
# of Pages:	21

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Thank you.

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type:	B
Meeting Category:	CMC End of Phase 2
Meeting Date and Time:	December 13, 2006 10:30-12:00 PM
Meeting Location:	Teleconference
Application Number:	10426
Product Name:	Ecallantide
Received Briefing Package	November 14, 2006
Sponsor Name:	Dyax Corporation
Meeting Requestor:	Aurelie Grienenberger
Meeting Chair:	Emily Shacter, Ph.D.
Meeting Recorder:	Akilah Green, Senior Regulatory Management Officer

Meeting Attendees:

FDA Attendees

Emily Shacter, Ph.D., Quality Review Team Leader, Office of Biotechnology Products, Division of Therapeutic Proteins

Kathy Lee, Ph.D., Quality Reviewer, Office of Biotechnology Products, Division of Therapeutic Proteins

Sally Seymour, M.D., Clinical Team Leader, Division of Pulmonary and Allergy Products, Office of Drug Evaluation II

Susan Limb, Ph.D., Clinical Reviewer, Division of Pulmonary and Allergy Products, Office of Drug Evaluation II

Akilah Green, Senior Regulatory Management Officer, Division of Pulmonary and Allergy Products, Office of Drug Evaluation II

Sponsor Attendees

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Eliana Clark, PhD, Director, Pharmaceutics, Therapeutics Manufacturing and Development, Genzyme

Susan Richards, PhD, Group Vice President, Immunology/Clinical Laboratory Science, Genzyme

1.0 BACKGROUND

Dyax submitted a Type B meeting request dated August 22, 2006, to gain agreement on aspects of their CMC program for BLA filing of Kalirev for the treatment of angioedema. Dyax's briefing package was dated November 14, 2006. Upon review of the briefing package, the FDA responded to Dyax's questions via fax on December 11, 2006. The content of that fax is printed below. Any discussion that took place at the meeting is captured directly under the relevant original response including any changes in our original position. Dyax's questions are in ***bold italics***; FDA's response is in *italics*; discussion is in normal font.

2.0 DISCUSSION

2.1 QUESTION 1

Question 1:

Dyax believes that he proposed comparability plan provided in Section P.2.5.1 will adequately demonstrate acceptability of the change in drug product manufacturer from (b) (4) to Hollister-Stier for commercial manufacture. Does the FDA agree with this proposal?

FDA response to question 1:

The plan is acceptable.

2.2a & b QUESTION 2a & b

Question 2:

The proposed commercial drug substance and drug product specifications and the approach for setting these specifications are provided in Sections S.4 and P.5, respectively.

2a. Does the FDA agree that the approach for establishing commercial specifications for drug substance (DS) is acceptable?

FDA response to Question 2a:

In general your approach is acceptable; however we have the following question and comments:

1. The endotoxin specification should be based on manufacturing experience. All of the lots produced using the commercial process has endotoxin levels of less than (b) Please revise your endotoxin specification accordingly.

2. Please explain why the pH specification has been (b) (4) from the EDEMA3 13 to the current acceptance criterion.

3. Please justify the specification for the RP-HPLC main peak + product related peaks (b) (4) when your manufacturing experience has been (b) (4).

4. Please justify the GP-HPLC specification of (b) when your manufacturing experience has been (b) (4)

DISCUSSION

Dyax indicated they will review the FDA's comments and propose to tighten the specifications. The original specification for pH was set arbitrarily with limited data and given a range (b) standard deviations. The FDA stated that the industry came up with that method and it is not something that the FDA advocates. Dyax's protein is less stable at (b) (4) pH. It does not make sense to (b) (4) The use of (b) standard deviations is not acceptable. Dyax should use a 95% CI, and do a statistical analysis to determine the specifications. This should be discussed with the statisticians. The FDA commented that we do not want Dyax to set the specifications too tight such as 7.1 $\pm$.1. Dyax stated that they agree with the FDA. However, (b) standard deviations is a standard calculation they are using. If they modify the specifications, Dyax suggested that they base it on the data they already have. Dyax noted that they filed an amendment regarding this.

In regards to the GP-HPLC assay, Dyax stated that there was an error in the table in the briefing package on pages 136-7. They added the GP-HPLC assay in 2005 and only have data for two lots. The GP-HPLC assay is now used as part of the release tests. The FDA noted that Dyax will not need to submit an amendment to the IND to set the specifications since they plan to submit a BLA. Specifications are determined at the time of BLA filing based on manufacturing, clinical experience, and process validation. The FDA told Dyax that if they are consistently producing lots with 99% purity by HPLC, then produce a lot with 95% purity by HPLC, they would need to understand why that lot is different and investigate the impact on the safety and efficacy of that lot. Specifications that are too broad allow bypassing this important assessment.

2b. Does the FDA agree that the approach for establishing commercial specifications for drug product is acceptable?

FDA response to question 2b:

In general your approach is acceptable; however, we have the following question and comments:

Please refer to comments 1 – 4 above. In addition, please explain why GP-HPLC was not performed on the DP when it is listed as a release test.

2.3 QUESTION 3

Question 3:

The proposed storage temperature and shelf life for commercial (b)) (4) ***respectively. The shelf life will be based on stability data from DS lots manufactured at*** (b) ***L*** (b) (4) ***at 36 months) and*** (b) ***L commercial scale*** (b ***lots with more than 24 months*** (b) (4) ***with at least 9 months) manufactured at***) ***Avecia (commercial manufacturer). Does the FDA agree that the anticipated DS stability package to support the*** (b) (4) ***acceptable?***

FDA response to question 3:

The proposed storage temperature and shelf-life plan is acceptable. In addition to the tabular stability data, please submit trend analysis on the stability data (e.g., 99/95% confidence interval trending).

DISCUSSION:

Dyax stated that they plan to submit their trend analysis on the stability data with 95% CI trending and they will submit it in the BLA. The FDA indicated that tabular data are acceptable, but we need a statistical analysis as well. In addition, there should be examples of raw data to assess the quality of the data. Dyax does not need to provide every chromatogram from each analysis. The raw data should be placed in a stability report with examples from time zero, the middle, and the end of stability testing. In the case of extensive degradation, additional raw data may need to be submitted. The raw data can be included in the product characterization section of the eCTD.

2.4a & b QUESTION 4a & b

Question 4:

The proposed storage temperature and shelf life for commercial drug product is 2°C to 8°C and 24 months, respectively. The shelf life will be based on stability data from a combination of drug product lots manufactured at (b) (4) ***(clinical drug product manufacturer) and at Hollister-Stier (commercial drug product manufacturer).***

Dyax is anticipating filing a rolling/advanced BLA submission, wherein the CTD Module 3 (CMC section) may be submitted several months in advance of the clinical (b) (4)

submission. Dyax anticipates having over 24 months real time data on three drug product lots produced at (b) (4) and at least 15 months real time data on three drug product lots produced at Hollister-Stier at BLA approval.

a. Does the FDA agree that the anticipated drug product stability package to support the proposed 24 month shelf life at 2°C to 8°C is acceptable for BLA filing?

FDA response to question 4a:

The proposed storage temperature and shelf-life plan is acceptable.

b. Does the FDA agree to the approach for advanced submission and updates of stability data?

FDA response to question 4b:

The plan is acceptable. As part of the BLA approval, you will be required to submit stability updates for the commercial product as the data become available.

2.5 QUESTION 5

Question 5:

Dyax is anticipating that the facility information for the drug substance and drug product contract commercial manufacturers, if not provided directly in the BLA, will be provided to the FDA as a Type V DMF. Does the FDA agree with this approach?

FDA response to question 5:

Please submit the information with the BLA so that the BLA is a stand-alone document.

DISCUSSION:

The FDA commented that Dyax can provide the data in a DMF and have a letter of authorization for us to review the manufacturer's DMF on their behalf. Dyax questioned if they could submit additional data regarding media fill with background data. The FDA stated that media fill data has to be reviewed by the Therapeutic Facilities Research Branch (TFRB), which is a different division. TFRB handles container closure issues, however, they typically do not review anything prior to BLA submission. Therefore, Dyax may not receive feedback on their submission.

2.6 QUESTION 6

Question 6:

The current antibody assay used to monitor antibody formation in Phase 2 EDEMA2 study and the Phase 3 EDEMA3 study were previously reviewed by the FDA and are discussed in Section A.4. To completely address the FDA comments on the current assays, new assay formats are under development (Section A.6) and will be validated according to ICH and industry guidelines for analytical procedure and method validation. Once validated, the new assay will be used to monitor antibody formation in the Phase 3 EDEMA4 study and the long term safety study, DX-88/19, as well as in DX-88/16 (b) (4) ***A comprehensive assessment of antibody data from all studies will be presented in the BLA submission. Does the FDA agree with this approach?***

FDA response to question 6:

We recommend that you submit the protocols to the FDA for review prior to BLA submission so that we can perform a comprehensive review and provide feedback if required. Please indicate the specificity, linearity, sensitivity, and reproducibility of the assays in your submission.

DISCUSSION:

Dyax stated that they will submit the immunogenicity assay without the neutralizing assay at the end of the second quarter of 2007 and welcome the FDA's feedback. The FDA indicated that that is acceptable. Dyax indicated that they will submit a meeting request for a quicker response although the standard is to submit it as an IND amendment. The assay will be used in the EDEMA4 study, which will start enrolling patients in February 2007. The FDA noted that Dyax should obtain serum samples, and freeze and bank them until the assay is optimized. However, Dyax does not have to have the FDA's feedback prior to using it if Dyax determines the assays are sensitive, reproducible, etc., and meets the FDA's public guidance on the subject.

2.7 QUESTION 7

Question 7:

(b) (4)

(b) (4)

FDA response to question 7:

You did not provide sufficient information about the assays for us to determine if either format is acceptable. Please describe in greater detail the two assay formats.

DISCUSSION:

(b) (4)

(b) (4)

(b) (4)

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

4.0 ACTION ITEMS

There were no action items identified during the meeting.

5.0 ATTACHMENTS AND HANDOUTS

The neutralizing assay format is attached.

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

Drafted by: Green/December 18, 2006

Initialed: Shacter/January 10, 2007, Lee/January 10, 2007

Finalized: Green/January 7, 2007

Linked Applications	Sponsor Name	Drug Name
IND 10426	DYAX CORP	Kallikrein Plasma Inhibitor (recombinant, Pichia pastoris, Avecia Biotechnology)

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/s/

AKILAH K GREEN
01/11/2007

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

Memorandum of Facsimile Correspondence

Date:	January 11, 2007
To:	Aurélie Grienenberger Associate Director, Regulatory Affairs
Company:	DYAX Corp
Fax:	(617) 225-2501
Phone:	(617) 250-5762
From:	Akilah Green, RN, MS Senior Regulatory Management Officer Division of Pulmonary and Allergy Products
Subject:	BB IND 10426; December 13, 2006, Meeting minutes
# of Pages:	15

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Thank you.

IND 10,426

MEMORANDUM OF MEETING MINUTES

MEETING DATE: August 29, 2006

TIME: 8:00 – 9:30 AM

LOCATION: Food and Drug Administration
White Oak, Building 22, Conference Room 1417
Silver Spring, Maryland 20993

APPLICATION: BB IND 10426/DX-88
Type B Meeting/EOP2

DYAX REPRESENTATIVES:

Tony Arulanandam, DVM, PhD, Senior Director, Pharmacology and Preclinical Development
Thomas Beck, MD, President and Chief Operating Officer
Peggy Berry, Senior Vice President, Quality and Regulatory Affairs
Henry Blair, Chief Executive Officer
Nicole D'Auteuil, Senior Director, Regulatory Affairs
Aurelie Grienenberger, PhD, Director, Regulatory Affairs
Tess Schmalbach, MD, PhD, Chief Medical Officer
Fayelle Whelihan, PhD, Senior Vice President, Program Management
Ivana Magovcevic-Leibsch, PhD, JD

Genzyme:

Alex Kuta, PhD, Vice President, Regulatory Affairs
Kerry Culm-Merdek, PhD, Staff Scientist II, Pharmacology & Toxicology
Bill Abernethy, Director, Global Commercial Strategy
Johan Frieling, MD, PhD, Senior Medical Director, Genzyme Europe BV
Henk Schuring, PharmD, Director, Regulatory Affairs Europe, Genzyme Europe BV

(b) (4)

(b) (4)

DIVISION OF PULMONARY AND ALLERGY PRODUCTS (DPAP) REPRESENTATIVES:

Badrul A. Chowdhury, M.D., Ph.D., Division Director
Lydia Gilbert-McClain, M.D., Clinical Team Leader
Sally Seymour, M.D., Acting Clinical Team Leader
Susan Limb, M.D., Clinical Reviewer
Robert Boucher, M.D., Clinical Reviewer
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Jean Wu, Ph.D., Pharmacology/Toxicology Reviewer
Emmanuel Fadiran, Ph.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 2, Office of Clinical Pharmacology
Ruthanna Davi, M.S., Biostatistics Team Leader, Office of Biostatistics, Division of Biometrics II
Jim Gebert, Ph.D., Biostatistics Reviewer, Office of Biostatistics, Division of Biometrics II
Tan Nguyen, M.D., Orphan Drugs
Akilah Green, M.S., R.N., Senior Regulatory Management Officer

BACKGROUND: Dyax submitted a Type B meeting request dated June 22, 2006, to gain agreement on your overall development program for DX-88 in the treatment of angioedema. Dyax's briefing package was dated July 31, 2006. Upon review of the briefing package, the Division responded to Dyax's questions via fax on August 25, 2006. The content of that fax is printed below. Any discussion that took place at the meeting is captured directly under the relevant original response including any changes in our original position. Dyax's questions are in ***bold italics***; FDA's response is in *italics*; discussion is in normal font.

Clinical

Question 1:
The sponsor has provided documentation regarding the creation, development, reliability and validation testing of the patient reported outcome (PRO) measure (Treatment Outcome Score [TOS]) that is to be relied upon, along with time to improvement and Mean Symptom Complex Score (MSCS), to determine efficacy of the product.

a. Does the FDA agree that these tools are relevant to the disease and appropriate for use as endpoints in the pivotal studies?

b. Does the FDA agree that the activities completed and planned for PRO validation are adequate for filing the BLA?

Division Response to 1.a.:
We agree that the Treatment Outcome Score [TOS] and the Mean Symptom Complex Score (MSCS) are relevant to the disease and appropriate to use as endpoints in the pivotal studies.

Note that the general claim of "improvement in symptoms associated with hereditary angioedema" would only be supported if analysis of scores revealed that the treatment effect is not reserved to a certain subset of symptoms complexes.

Division Response to 1.b.:
(i) You plan to complete cognitive debriefing interviews with the revised instrument to establish content validity. These interviews should not only test for readability, comprehension, interpretability, navigability and usability, but also should

provide documentation that patients understand the concept of a "symptom complex" and are able to provide a valid self-assessment of each symptom complex during the time that they are experiencing symptoms. In particular, can patients understand the type and location of "redness, rash, or itching" that is being queried for each symptom complex? If patients experience multiple symptoms in a complex, can they meaningfully integrate them into one score?

(ii) *Patients should be trained in the use of the instrument at the time of enrollment so that they are familiar with it when they present for study treatment. This may overcome some of our content validity concerns. Document and submit investigator and patient training materials.*

(iii) *Submit translations of the measurement instrument along with evidence of the adequacy of the translation and cultural adaptation process, if you plan to enroll non-US English-speaking patients into this trial.*

(iv) *We remind you that understanding the usefulness and determination of the measurement properties of a composite endpoint (in this case, an index) is an iterative process that evolves over time. Rules for interpretation of composite measures depend on substantial clinical experience with the measure in the clinical trial setting. Because that is not possible in this instance, you should be aware that experience with these measures in the clinical trial may generate interpretation issues that we have not identified at this point.*

(v) *Refer to the* Draft Guidance for Industry on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims, *available at www.fda.gov/cder/guidance/5460dft.pdf. Section V.F. of that document lists specific concerns when using electronic PRO instruments. You should plan carefully to ensure that FDA regulatory requirements are met for sponsor and investigator record keeping, maintenance, and access. (See also 21 CFR 312.50, 312.58, 312.62, 312.68, 812.140. and 812.145.)*

Discussion:
Dyax stated that they will take into consideration our comments and asked if the Division would be willing to look over their plan before they launched the cognitive debriefing protocol. The Division instructed Dyax to submit the protocol for review and indicated that it typically takes us 45 days to review protocols, however, this may take longer since we would have to consult another group.

Question 2:
The sponsor plans to conduct a confirmatory dose justification and efficacy study (EDEMA4) with 2 subcutaneous doses of ecallantide, which will also define the pharmacokinetics of (b) (4) ***in hereditary angioedema (HAE) patients during a moderate to severe acute attack, and provide confirmatory blinded randomized efficacy data. The sponsor believes that the results of this trial will confirm that the 30 mg***

subcutaneous dose is a safe and effective dose to commercialize. Does the FDA agree with this plan and proposed study design?

Division Response:
We agree with your plan to conduct a confirmatory study to evaluate the 30 mg SC dose. However, you should include a placebo arm in your design with a superiority comparison of the 30 mg dose. Since the 5 mg dose is expected to have some effect as well, including this dose in the study without a placebo will not fulfill this objective.

See our response to questions 3 and 4.

Discussion:
Dyax noted that they agree to include a placebo arm in their study and they plan to continue with their current practice of naive patients. In addition, based on the difficulty they are experiencing enrolling patients, they proposed to include a smaller number of patients in the 5 mcg arm. Dyax indicated that their objective for the 5 mg arm is to include it for dose-ranging. The study will be powered based on a comparison of 30 mg and placebo. The Division stated that the dose ranging that has been done with the IV formulation is adequate given the comparative exposure (AUC) of the IV and the SC formulations. Therefore it is not necessary to include the 5 mg dose. The comparison should be 30 mg to placebo.

Question 3:
Given the validation component in the EDEMA3 data analysis, the sponsor proposes to provide additional, confirmatory efficacy for ecallantide in a 2-arm, dose-controlled study of 40 attacks (20 per arm) [EDEMA4]. Does the FDA agree with this plan and proposed study design?

Division Response:
We agree with the conduct of a confirmatory efficacy study. See our response to questions 2 and 4.

Question 4:
Based on the rarity of the disease, the difficulty in recruiting eligible patients and the fact that substantial numbers of patients with this orphan disease have been enrolled in other studies, the sponsor is proposing that enrollment and analyses in the planned clinical study (EDEMA4) be based on unique angioedema attacks rather than unique patients. Does the FDA agree with this proposal?

Division Response:
No, we do not agree with your proposal that the analyses be based on unique angioedema attacks rather than unique patients.

A single patient's response to multiple attacks and treatment of those attacks would likely be positively correlated thus violating the fundamental statistical assumption of independence between observations. Positive correlation among observations which

have been assumed to be independent in the statistical calculations in essence would lead to artificially inflated power for the associated hypothesis testing. In addition, subjects who experience a favorable outcome to study treatment with the first attack would likely be more willing to enroll in the study a second time possibly leading to a biased study sample including multiple measurements of specific subjects who are predisposed to doing well with study treatment.

The unit of observation for this study should be at the patient level. Revising the primary efficacy analysis to a superiority comparison of 30 mg (b) (4) *to placebo as suggested in the response to question 2 will require a smaller sample size than what is required for a superiority comparison of 30 mg* (b) (4) *to 5 mg* (b) (4) *as proposed in the meeting package, assuming that 5 mg* (b) (4) *would be at least slightly more effective than placebo.*

Question 5:
Does the FDA agree that a BLA submission for 30 mg subcutaneous ecallantide for the treatment of hereditary angioedema, which contains data from the clinical studies described herein, may, depending on the results of these studies, be acceptable for filing?

Division Response:
The studies described in your briefing document may be used for filing a BLA.

Question 6:
The BLA for ecallantide will include a total of 11 clinical studies, including 3 pivotal trials (EDEMA1, EDEMA3, and EDEMA4). Does the FDA agree that this data package will be sufficient to support a BLA filing from the standpoint of evaluating efficacy of ecallantide for the desired indication?

Division Response:
The data package with the clinical studies outlined may be sufficient to evaluate efficacy taking into account our responses to questions 2, 3, and 4.

Question 7:
The BLA for ecallantide will include a total of over 220 unique subjects and patients having been given over 500 doses with the highest total number of doses given to a single patient (to date) being 18, over a period of 20 months. The highest dosing frequency of any individual patient to date has been slightly more often than monthly (9 attacks over a period of 8 months). Intermittent, repeat dosing of patients will continue to be studied through approval (Continuation Protocol). Does the FDA agree that this safety database will be sufficient to support a BLA filing?

Division Response:
The open-label study should have a defined duration and the sample size should be increased. The proposed sample size of 30 patients is too small. Patients should have antibody testing throughout the duration of the study.

The proposed safety database may be sufficient to support a BLA filing, provided no new safety signals emerge in the ongoing EDEMA3 and the planned EDEMA4 and open-label safety study.

Discussion:
Dyax noted that they are collecting multiple dose data for all patients including those in EDEMA3 and will continue through the filing of the BLA. They have 60 patients with multiple exposures and intend to revise and update their figures in the pre-BLA package. Dyax further noted that the open label study is not using a compassionate use protocol. It includes modified criteria which allows for continued access. With regard to the small sample size, Dyax is looking at patients in EDEMA1. The Division stated that the 60 patient sample size is probably not reasonable and questioned how many patients will use DX-88 once it is approved. This is a small number to make an assessment on. Although we understand that the patient population with this disease is small, it is hard to approve a drug based on such a small exposure. The Division further pointed out that if Dyax expects around only 500 patients to use the drug then the number of patients exposed would not invoke the ICH numbers for long term safety. However, Dyax needs to make a reasonable attempt to get as many patients as possible exposed to the drug. Dyax indicated that they would make every attempt to get more patients and questioned if keeping the study open until approval of the product would be too long. The Division commented that it would depend on when the submission comes in. It is possible that the open-label safety study may become an individual patient study. We would like to see antibody testing as long as the patient is on the product.

Question 8:
Does the FDA agree that if, upon review, the FDA finds the data in these trials to be positive, then the FDA will likely find that there is adequate evidence of treatment benefit to support approval of this BLA, pending review of the drug's safety profile and manufacturing issues?

Division Response:
The determination of adequate evidence of treatment benefit to support approval is a review issue.

Non-Clinical Question:

Question 1:
Does the FDA agree that these complete studies, assuming that the results are conclusive, will provide an adequate pharmacologic and toxicological profile of the product to support this BLA filing?

Division Response:
Based on IC50 values, it can not be concluded that the rat is not a relevant species for toxicity assessment. Given the severe toxicity in the rat IV studies and lung edema in the

minipig study (Study No. (b) 44605), you should assess the chronic toxicity in the second species in addition to monkey. We recommend that you conduct a 4-week rat study and a 4-week minipig study to determine the second species.

Chronic (6-month) studies in two species are required to support the approval of Ecallantide, which is indicated for intermittent use for an indefinite duration.

Provide justification for not conducting carcinogenicity studies of Ecallantide.

Discussion:
Dyax indicated that they acknowledge the need for chronic toxicity studies and proposed to conduct one rodent and one non-rodent chronic toxicity studies per ICH guidance. Initially, they proposed to conduct a 6-month toxicity study in rats and determine a non-rodent species between minipig and monkey for the chronic study by conducting a 4-week repeat dose study in minipigs. The Division agreed with Dyax performing 6-month studies in two species. In addition to a chronic toxicity study in monkeys, the selection of the second appropriate species for a chronic study between rat and minipig is warranted due to the findings in the rat and minipig studies. The Division also pointed out that per ICH guidance, the two species requirement for toxicity studies should be understood as one of two species should be a non-rodent species. Then, Dyax indicated that they would plan to conduct a 6-month toxicity study in monkeys and a 6-month study in rats, and provide justification based on available information to select rat as the second species.

Dyax proposed to use a dosing regimen of once weekly in the preclinical chronic toxicity studies. The Division indicated that the pre-clinical study dosing frequency should reflect and support the clinical dosing regimen, which is every 72 hours in the proposed clinical studies. Dyax stated that the current dosing frequency based on the clinical experience is every three weeks and the frequency of attacks is between six and twenty per year. The Division emphasized that the dosing frequency in preclinical studies should be the same or more than the most anticipated clinical setting for the indication. Dyax could submit the justification for not conducting carcinogencity studies in the original IND submission for comment and should submit all final preclinical study reports in the BLA.

Regulatory Questions:

Question 1:
Does the FDA have any additional, general comments or guidance to provide on the targeted product information?

Division Response:
Your proposed indication states "Indicated for the treatment of hereditary angioedema." However, your development program is targeted for the treatment of acute attacks of hereditary angioedema. The indication should be consistent with the aspect of the disease studied. Additional comments on the label are premature at this time.

Question 2:
The sponsor plans to study patients as young as 10 years of age in the proposed clinical studies. Based on the age distribution of the disease, generally involving patients above age 10, the sponsor plans to request a pediatric waiver for patients younger than 10 years of age. Does the FDA anticipate that a waiver would be appropriate?

Division Response:
Submit your request for a wavier with your rationale at the time of BLA submission. A decision on pediatric wavier is made after the BLA submission. Refer to the draft guidance for industry "How to comply with the Pediatric Research Equity Act."

Question 3:
The sponsor would like to maintain the Fast Track Designation for ecallantide in the treatment of hereditary angioedema patients and would be willing to file a separate request for the designation if necessary. Could the FDA comment regarding the acceptability and requirement(s) of this request?

Division Response:
We concur that hereditary angioedema is a rare disease and the ability to study any one attack type is limited by the presenting patient population. It is reasonable to submit a new request for Fast Track Designation.

Discussion:
Dyax questioned if it would be acceptable to use the endpoints for the pivotal protocol. The Division stated that it is acceptable.

Additional Discussion:
Dyax proposed to do a rolling CMC submission around the pre-BLA meeting. The Division stated that we can hear Dyax's proposal and make a decision then. There is an ongoing Pilot 1 and 2 project that Dyax is not a part of. However, we will consider the proposal as Dyax finalizes the efficacy study. The Division pointed out that Dyax can choose to use the Special Protocol Assessment (SPA) route to submit the efficacy study, which will allow us to review and comment on their protocol in 45 days. If Dyax wants the PRO group to look at their data separately, they can submit it for review. However, Dyax should submit the PRO piece prior to submitting the SPA request.

Drafted by:	Green/September 9, 2006
Initialed by:	Gilbert-McClain/September 12, 2006, Wu/September 15, 2006, Sun/September 15, 2006, Chowdhury/September 21, 2006
Finalized:	Green/September 21, 2006

Linked Applications	Sponsor Name	Drug Name
IND 10426	DYAX CORP	Kallikrein Plasma Inhibitor (recombinant, Pichia pastoris, Avecia Biotechnology)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AKILAH K GREEN
09/21/2006