CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125338

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/10
See OMB Statement on Page 3.

NDA NUMBER
125338/0/0

NAME OF APPLICANT/NDA HOLDER
Auxilium Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
XIAFLEX™

ACTIVE INGREDIENT(S)	STRENGTH(S)
Clostridial collagenase including collagenase AUX-I & collagenase AUX-II	0.58 mg

DOSAGE FORM
Lyophilized powder for injection after reconstitution.

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
RE39941	Dec. 18, 2007	Aug. 22, 2014

d. Name of Patent Owner	Address *(of Patent Owner)*	
Advance Biofactures Corporation	35 Wilbur Street	
	City/State: Lynnbrook, New York	
	ZIP Code: 11563	FAX Number *(if available)*
	Telephone Number: (516) 593-7000	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) ☞	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☑ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☑ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☑ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☑ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☑ Yes	☐ No
4.2 Patent Claim Number(s) *(as listed in the patent)* 1-15 and 17-43	Does (Do) the patent claim(s) referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☑ Yes	☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)* Treatment of advanced Dupuytren's Disease		

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Benjamin J. Del Tito, Jr.	13 Feb 2009

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☑ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Benjamin J. Del Tito, Jr., Ph.D.	
Address 40 Valley Stream Parkway	City/State Malvern, PA.
ZIP Code 19355	Telephone Number (484) 321-5989
FAX Number *(if available)* (610) 279-8620	E-Mail Address *(if available)* bdeltito@auxilium.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html.*

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

1.3. Administrative Information

PATENT CERTIFICATIONS

Auxilium Pharmaceuticals, Inc., hereby acknowledges that the provisions of 21 U.S.C 355(b)(2) or (j)(2)(A) do not apply to this biologics license application, BLA #125338/0/0

Auxilium Pharmaceuticals, Inc., hereby certifies US Patent No. RE39941 covers the method of using the pending drug product for which approval is being sought that is claimed by the patent. AA4500 (XIAFLEX™, Proposed Trade Name) is the subject of this application for which approval is being sought.

Benjamin J. Del Tito, Jr., Ph.D.

Senior Vice President – Quality and Regulatory Affairs

11 Feb 2009

Date

EXCLUSIVITY REQUEST

Sponsor hereby claims seven (7) years exclusivity, under 21 CFR 316.31(a), from the date of approval of this BLA for XIAFLEX™ (Proposed Established Name). Orphan drug designation was made on May 23,1996, to Lawrence C. Hurst, M.D. for the designation of Clostridial collagenase as an orphan drug (application #95-925) (Appendix 1.3.5.3.1). Ownership of orphan drug designation for this drug was transferred to Sponsor by letter dated December 12, 2005, in accordance with 21 CFR 316.27 (Appendix 1.3.5.3.2). Transfer was accepted by the Sponsor, and notification made to the Office of Orphan Products Development by letter dated December 14, 2005 (Appendix 1.3.5.3.3). Acknowledgement of transfer of orphan drug designation to the Sponsor by the Office of Orphan Products Development was made by letter dated May 8, 2006 (Appendix 1.3.5.3.4).

1.3. Administrative Information

3. DEBARMENT CERTIFICATION

Auxilium Pharmaceuticals, Inc., hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) and 306(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 335(a) and (b)) in connection with this application for XIAFLEX™, Proposed Name (AA4500; Clostridial collagenase for Injection).

Benjamin J. Del Tito, Jr., Ph.D.

Senior Vice President – Quality and Regulatory Affairs

22 Jan 2009

Date

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

~~NDA~~/BLA#: 125338 | Supplement Number: _____ | NDA Supplement Type (e.g. SE5): _____

Division Name: Division of Anesthesia, Analgesia and Rheumatology Products | PDUFA Goal Date: 08/28/2009 | Stamp Date: 02/27/2009

Proprietary Name:

Established/Generic Name: Clostridial Collagenase

Dosage Form: injection

Applicant/Sponsor: AuxiliumPharmaceuticals, Inc.

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: for the non-surgical treatment of advanced Dupuytren's disease.

Q1: Is this application in response to a PREA PMC/PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMC/PMR #:_____

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

☐ Yes. Please proceed to Section D.

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

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

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

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

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

Q3: Does this indication have orphan designation?

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

☐ No. Please proceed to the next question.

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

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply.
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

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

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

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

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

☐ Justification attached.

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

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

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible[#]	Not meaningful therapeutic benefit*	Ineffective or unsafe[†]	Formulation failed[Δ]
☐	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, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

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

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

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	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):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	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 pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

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

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

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	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.

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} 3/20/2009

Regulatory Project Manager

Margarita Tossa

(Revised: 6/2008)

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

Xiaflex PMR#1 - Immunogenicity

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

BLA# 125338

PMR/PMC Description: An *in vitro* study of human sera from patients who have received multiple Xiaflex injections to evaluate the potential for cross-reactivity of anti-product antibodies (i.e., anti-AUX-I and anti-AUX-II) with endogenous human MMPs (including MMP-1, MMP-2, MMP-3, MMP-8, and MMP-13) with similar homology and relevance to the protein components of Xiaflex. This study should assess the frequency of inhibition of the enzymatic activity of these human proteins by anti-product antibodies and by neutralizing anti-product antibodies. This study should also be designed to assess whether repeated treatment courses of Xiaflex injection result in anti-product antibodies that are more persistent and cross-reactive to endogenous proteins compared to initial anti-product antibody responses.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	03/31/2010
Study/Clinical trial Completion Date:	06/30/2010
Final Report Submission Date:	12/31/2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

Since the protein components in Xiaflex have some sequence homology with human MMPs, anti-product antibodies to the protein components of Xiaflex could theoretically interfere with these human proteins. Since there was no clear evidence that the frequency, titers, or neutralizing status of anti-product antibodies was associated with adverse events, this should not prevent approval of the BLA.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

See "PMR/PMC Description" above

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

See "PMR/PMC Description" above

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☒ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☒ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
Sera from patients previously treated with Xiaflex with high anti-product antibody titers at a single time point in the controlled or uncontrolled portions of Studies AUX-CC-854, AUX-CC-856, AUX-CC-857, AUX-CC-858, or AUX-CC-859 can be used for this PMR.
☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☒ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

   ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
   ☒ Are the objectives clear from the description of the PMR/PMC?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Xiaflex PMC#2 - Excess Fill Volume

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

BLA#125338

PMR/PMC Description: To evaluate the minimal fill volume required for appropriate dosage withdrawal and assess patient risk of overdose.

PMR/PMC Schedule Milestones: Fill volume feasibility findings 03/31/2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☒ Theoretical concern
   - ☐ Other

There is a risk of overdosing from the excess fill volume after reconstitution. The clinical risk is the possibility of tendon ruptures in patients receiving excess drug. No documented occurrence of tendon ruptures during the clinical trials were attributed to overdosage, hence the risk is theoretical. Some liquid remains in the stopper after inversion of the vial for withdrawal. The level of reconstituted liquid is too low in the vial to be withdrawn without inversion of the vial, hence the risk for pooling of vials is low. This is not an approvability issue because the risk for overdosing is theoretical.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

In the BLA amendment #32, Auxilium provided two items as a rationale for their excess volume. First, they cited complaints received by the original sponsor (BTC) who used to have (b) (4) (its now 0.9 mg) from clinicians that it was very difficult to remove the required dosage volume from the vials. They claim BTC did a study to determine that (b) (4) mg of lyophilized powder was required for ease of withdrawal. Secondly, Auxilium conducted a study where they measured the actual excess volume that could be withdrawn after removal of dosage. The actual excess volume (b) (4) was less than the theoretical excess (b) (4) (b) (4) The actual excess volumes translate into (b) (4) of excess relative to single dose volume (b) (4) (b) (4) Hence, the risk for overdosage (accidental or intentional) might still exist. USP recommends an excess of no more than 10-15% depending on the total volume and viscosity of the drug.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

See "PMR/PMC Description".

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other
Investigation on the excess fill volume issue and proposed path forward.

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Xiaflex PMC#3

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

BLA #125338

PMR/PMC Description: Conduct a study to demonstrate microbial control at the end of hold (10 days) for the individual AUX-1 and AUX-II intermediates.

PMR/PMC Schedule Milestones: Final Report Submission Date: 12/31/2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☒ Other

(b) (4)

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Not applicable

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

See "PMR/PMC Description" above

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

_____

Agreed upon:

- ☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

_____

Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

Xiaflex PMC#4

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

BLA #125338

PMR/PMC Description: Qualify the bioburden test for in-process intermediates. The qualification should be performed using three different lots.

PMR/PMC Schedule Milestones: Final Report Submission Date: 12/31/2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☒ Other

The applicant stated in the e-CTD amendment sequence 0005 that the validation for process intermediates and formulation buffer for bioburden testing were ongoing and that the BLA would be updated when these studies are completed. This is not an approvability issue because the qualification of the bioburden specification test for the drug substance was qualified using three drug substance lots. The PMC is intended to ensure the completion of these studies of the in-process intermediates.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Not applicable

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

See "PMR/PMC Description" above

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Xiaflex PMC #5

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

BLA #125338

PMR/PMC Description: Qualify the endotoxin test on an additional two lots each of AUX-I intermediate, AUX-II intermediate, and drug substance, and three lots each of HIC eluate and TFF-1 concentrate.

PMR/PMC Schedule Milestones: Final Report Submission Date: 12/31/2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

The applicant stated in the e-CTD amendment sequence 0005 that the endotoxin qualification for process intermediates for endotoxin testing was ongoing and that the BLA would be updated when these studies are completed. This is not an approvability issue because data were provided for one lot of drug substance. The PMC is intended to ensure the completion of these studies with three lots of the various intermediates and bulk drug substance.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Not applicable

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

See "PMR/PMC Description" above

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Xiaflex PMC #6

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

BLA #125338

PMR/PMC Description: Conduct and submit data from an adequate container-closure integrity study for the diluent product with container-closure components that have been subjected to the same or worse (b) (4) cycle. The proposed (b) (4) test protocol and method for stability testing can be used to fulfill this requirement. Provide (b) (4) test validation results for container-closure integrity testing of lyophilized product and diluent vials in the stability program. Submit validation report and data.

PMR/PMC Schedule Milestones: Final Report Submission Date: 3/31/2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

The conditions for the microbial ingress test submitted in the BLA were not deemed to be sufficiently challenging. (b) (4)

(4)

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

See PMR/PMC Description.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

See "PMR/PMC Description" above

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Xiaflex PMC #7 - DMPQ

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

BLA #125338

PMR/PMC Description: Determine the D121-value of the biological indicator G. *stearothermophilus* in the diluent product solution and reassess the validation studies conducted. Provide a comparison to the D121-values used in the product validation studies. Submit data in a CBE supplement by March 2010.

PMR/PMC Schedule Milestones: Final Report Submission Date: 3/31/2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☒ Other

(b) (4)

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

See "PMR/PMC Description"

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

See "PMR/PMC Description" above

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

Xiaflex PMC #8 - Immunogenicity

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

BLA #125338

PMR/PMC Description: To demonstrate the feasibility of an *in vitro* study of human sera from patients who have received multiple Xiaflex injections to evaluate the potential for cross-reactivity of anti-product antibodies (i.e., anti-AUX-I and anti-AUX-II) with two endogenous human proteins, polycystin 1 and KIAA0319, and propose a path forward.

PMR/PMC Schedule Milestones: Final Report Submission Date: 12/31/2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☒ Theoretical concern
   - ☐ Other

Since the protein components in Xiaflex have some sequence homology with two endogenous human proteins, polycystin 1 and KIAA0319, anti-product antibodies to the protein components of Xiaflex could theoretically interfere with these human proteins. Since there was no clear evidence that the frequency, titers, or neutralizing status of anti-product antibodies was associated with adverse events, this should not prevent approval of the BLA.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

See "PMR/PMC Description" above

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

See "PMR/PMC Description" above

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other
immunogenicity *in vitro* feasibility study

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Xiaflex PMC#9 – Host Cell Protein Assay

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

BLA # 125338

PMR/PMC Description: To demonstrate feasibility of an immune-based host cell protein assay and to propose a path forward.

PMR/PMC Schedule Milestones: Assay development findings 12/31/2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☒ Theoretical concern
   - ☐ Other

(b) (4), the Sponsor should incorporate a validated ELISA as soon as feasible. While this is an important product quality issue it should not hold up approvability because of two main reasons. First, Auxilium has a crude but qualitative assay for detecting host cell proteins by SDS-PAGE gel and silver staining and sufficent manufacturing controls to provide some added assurance of product quality with regard to these impurities. Second, the data and discussion provided by Auxilium demonstrates the technical difficulty in developing an immune-based HCP assay for clostridial proteins.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

(b) (4)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

(b) (4)

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other
Development of immune-based assay to detect host cell proteins

5. Is the PMR/PMC clear, feasible, and appropriate?

   ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
   ☒ Are the objectives clear from the description of the PMR/PMC?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Xiaflex PMC#10 – Subvisible Particles

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

BLA # 125338

PMR/PMC Description: To characterize the types and amounts of subvisible particles (b) (4) the drug product under stress conditions, at release, throughout the dating period, and to propose an appropriate control strategy, based on the risk to product quality.

PMR/PMC Schedule Milestones: Report of Characterization findings 06/30/2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☒ Theoretical concern
   - ☐ Other

This is not an approvability issue because the risk to changes in product quality due to subvisible particles is very low provided major manufacturing changes are not implemented, as the current process is well controlled and should meet the expected product performance. Auxilium also set a (b) (4) particules that provides limited control while information on this potentially critical product attribute is obtained. It should be noted that there is already a robust immune reponse to this product so an augmentation of this response is not expected.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

FDA currently does not have a guidance on setting limits for subvisible particles but believes a risk assessement should be performed on a case by case basis. There is a theoretical risk of enhanced immunogencity from increased levels of subvisible particles that can not be detected by SEC-HPLC and are not specified under USP <788> particulate testing used by the Sponsor. The applicant does not have sufficient historical data to assess the risk to product quality or set a tighter specification at this time. Auxilium set this specification based on batch analysis of 6 lots of DP.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The Sponsor proposes to initially characterize the (b) (4) sub-visible particles in DP under (b) (4) and provide the Division with a report plus a proposed path forward in June, 2010. A subsequent study that (b) (4) sub-visible particles content throughout the dating period as well as an appropriate control strategy would initiate after consultation with the Division.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other
Characterization of the 2-10 um sub-visible particles in drug product under stress conditions for the purpose of setting an appropriate release specification.

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Xiaflex PMC #11 – Individual Acceptance Criteria for Intermediates

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

BLA # 125338

PMR/PMC Description: To establish individual acceptance criteria for AUX-I and AUX-II profile and their mass ratio for the RP-HPLC for release and stability testing of the drug substance and drug product.

PMR/PMC Schedule Milestones: New assay and acceptance criteria 09/30/2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☒ Theoretical concern
   - ☐ Other

AUX-I and AUX-II are intended to be at equal mass ratio (b)(in the final drug product for achieving a synergistic effect. However, there is no control for the levels of individual enzyme after mixing. Sponsor should establish individual acceptance criteria for AUX-I and AUX-II HPLC profile and their mass ratio. It is not an approvability issue because control over individual enzymes is not the basis for the final product's biological activity. It is the synergistic action of the two enzymes on collagen, which is controlled in part by the potency assay. (b) (4) .

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

For drug substance, the ratio of the two peaks, (b) (4), should be developed as acceptance criteria. Sponsor should set specifications for each peak (b) (4)I (b) (4). Additionally, the specification for the RP-HPLC assay will need to be modified to account for the (b) (4) and any other unexpected peak. If the peak is present the batch will need to be investigated and potentially discarded.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Using a RP-HPLC method, the Sponsor has provided in-process limits for the DS as described in sequence 0028 of the eBLA. In a similar manner, they propose to establish acceptance criteria for the DP by March, 2010. The formal validation of the method and establishment of acceptance criteria will occur through June, 2010. The Sponsor proposes to submit an updated assay and acceptance criteria in September, 2010. Ongoing stability protocols will be updated to include the new assay and acceptance criteria by end of September, 2010.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other
Updated RP-HPLC assay and acceptance criteria for AUX-I and AUX-II

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Xiaflex PMC#12 – RP-HPLC Protein Recovery

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

BLA # 125338

PMR/PMC Description: To calculate the protein recovery for each HPLC method validation (SEC and RP-HPLC) using an orthogonal protein measurement assay that provides added assurance that the method is suitable for its intended purpose.

PMR/PMC Schedule Milestones: Assay development findings 12/31/2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☒ Theoretical concern
   - ☐ Other

This is not an approvability issue because all other parameters for the method validations were acceptable and the assays are in general suitable for their intended purpose. However, this commitment will provide better assurance that the results are accurate..

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The calculation for protein recovery for the HPLC assays was not performed using an orthogonal protein measurement assay. It is important to understand the amount of protein that is recovered in these separation techniques because a lower then normal recovery might indicate some product variants are not monitored in this analytical technique. A orthogonal measurement ensures the accuracy of the test as part of the method validation.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Protein recovery for each HPLC method validation will be tested using an orthogonal method to assure system suitability and in particular accuracy of the results. .

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other
Protein recovery from each HPLC method.

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Xiaflex PMC#13 – RP-HPLC Potential Impurities

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

BLA# 125338

PMR/PMC Description: To develop and validate the RP-HPLC method to quantify potential impurities for AUX-I intermediate, drug substance, and drug product.

PMR/PMC Schedule Milestones: Assay development and validation 12/31/2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☒ Theoretical concern
   - ☐ Other

The method for the RP-HPLC assay currently involves (b) (4) Furthermore, the current method is rather insensitive for detecting impurities. This is not an approvability issue because other assays are designed to detect specific impurites and potency is a sensitive measure of the API. Still, the ability to detect unexpected impurities and to accurately quantitate the APIs is a critical control system that should be implemented.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The need to better quantify impurities that may exist when (b) (4) The goal of this study will be to be able to quantify the individual impurities either by modification of the RP-HPLC assay or implementation of a different assay. This could be achieved by using higher amounts of material during (b) (4) or implementing a more sensitive assay.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

(b) (4)

[redacted]

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other
Development of (b) (4) for detecting impurities.

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Xiaflex PMC#14 – SDS Page Validation

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

BLA# 125338

PMR/PMC Description: To establish and validate a staining and destaining control (e.g., BSA) for SDS-PAGE Coomassie and Silver Stain to ensure appropriate level of detection for product or process related impurities.

PMR/PMC Schedule Milestones: Assay validation 2/28/2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☒ Theoretical concern
   - ☐ Other

This is not an approvability issue because the current assay has been shown to provide a sufficient level of detection when performed appropriately and additional tests for purity (RP-HPLC) and potency provide an additional indication of product quality. However, the procedures used in performing this test may alter assay sensitivity and therefore a routeine control should be implemented to ensure adaquate sensitivity on a test to test basis. Prior to using the updated assay, Auxilium will need to revalidate the assay and uptake the system suitability controls. .

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The current method for the SDS-PAGE assay does not appropriately control for variability in staining and destaining times. They also needed to provide the revised and finalized SOP for both (b) (4) SDS-PAGE methods. It must include the (b) (4) as an acceptance criteria and staining/destaining controls.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The Sponsor has committed to the inclusion of a staining and destaining control (protein) marker as part of the SDS-PAGE Coomassie method by December, 2009 as communicated in sequence 0028 of the eBLA. Currently, this approach is already captured in the SDS-PAGE Silver Stain test method (Test Method 30-2-0022 v 1 was submitted in sequence 0010 of the eBLA).

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other
Validation of revised SDS-PAGE method

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Xiaflex PMC#15 – Accuracy of SEC-HPLC

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

BLA# 125338

PMR/PMC Description: To confirm the accuracy of the SEC-HPLC method for detecting aggregates using stress samples (e.g., light, heat, oxidation) using orthogonal test methods (e.g., AUC or FFF).

PMR/PMC Schedule Milestones: Assay development findings 06/30/2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

When considered in the totality of their current testing scheme and proposal for including (b) (4) for aggregate testing, this deficiency is addressable after approval. This issue does not affect approvability because the Sponsor has provided some characterization data on the aggregate content, has a well controlled process and currently employs two assays that are capable of detecting high-molecular weight species, namely SDS-PAGE (b) (4)) and SEC-HPLC (for aggregates). In general SEC has been shown to be a robust and accurate assay for measuring protein aggregates however the assay has known limitations for detecting certain types of aggregates and should be evaluated for its suitability for every product.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Auxilium currently uses SEC-HPLC as their aggregate test method. Auxilium has stated that they are developing (b) (4) as orthogonal testing methods. While not as sensitive as AUC or FFF methods, these method will be acceptable as an orthogonal method and should be a PMC. The PMC should include information on showing equivalency between the SEC and (b) (4) or other proposed methods. The orthogonal method should be able to detect high molecular weight aggregates in a quantitative manner. (b) (4)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The Sponsor proposes to characterize stress-induced aggregates by AUC and additionally, estimate the linearity and/or LOQ of the characterized aggregates by SEC-HPLC. The Sponsor will submit the requested study report in June, 2010.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other
Development of orthogonal testing method for aggregates

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Xiaflex PMC#16 Immune Based Identity Assay

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

BLA# 125338

PMR/PMC Description: To develop and validate an immune-based identity assay and to add the validated assay to the release specifications for the drug substance and drug product.

PMR/PMC Schedule Milestones: Assay development findings 12/31/2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☒ Theoretical concern
   - ☐ Other

This is not an approvability issue because Auxilium currently has an RP-HPLC based method to identify AUX-I and AUX-II peaks and several methods that in totality will uniquely identify the product produce given the current manufacturing locations and current list of products manufactured at these sites. They will also be revising their acceptance criteria to account for AUX-I and AUX-II peaks (b) (4)

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Auxilium has an RP-HPLC assay as the primary identity test. Auxilium was informed that SDS-PAGE is not a reliable identity test. It is ideal to use an identity test that detects primary structure of proteins (such as Western blot, ELISA or peptide mapping). They were advised to use an orthogonal immune-based assay since they have antibodies. During PAI, Auxilium confirmed that they have antibodies for AUX-I and AUX-II.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The Sponsor proposes to validate an immune-based identity assay and include this identity test to the release specifications for drug substance and drug product. The target delivery date for the supplement is December, 2010

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other
Development of orthogonal identity immune-based testing

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Xiaflex PMC#17 – Annual Accelerated Stability

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

BLA# 125338

PMR/PMC Description: To include an accelerated or stress stability condition as part of the annual stability program for the drug substance and drug product.

PMR/PMC Schedule Milestones: Updated stability study report 06/30/2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☒ Theoretical concern
   - ☐ Other

Because this requirement involves the design of a study to be implemented next year, this study can be submitted following approval and can therefore be requested as a PMC.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The sponsor will submit real time stability data as an annual report for a request for extension of shelf-life. The purpose of an annual stability study is not to reevaluate the dating period but rather confirm that all the process changes (including personnel) made during the last year had no impact on product quality. Since a stability study performed at -70C is expected to have limited ability to detect significant changes that might affect product quality; the sponsor should include an accelerated or stress stability study that would be more sensitive to small but significant changes in product quality.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The Sponsor proposes to include a stress stability condition as part of the annual stability program. In particular, a -20°C condition for drug substance and a 25°C (b) (4) condition for drug product will be included. The stress stability studies will be implemented in the June, 2010 annual stability program.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other
Stressed stability testing as part of annual stability testing.

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Hilfiger, Christopher

From: Diak, Peter
Sent: Friday, December 04, 2009 4:08 PM
To: Diak, Peter; Hilfiger, Christopher
Cc: Choi, Lauren Y; Milburn, Cherye; Wheeler, Chris; Brodsky, Eric
Subject: RE: PSC

Chris,

If you still need a statement for the PSC from us...

"OSE's safety concerns are consistent with the medical reviewer's safety review of Xiaflex. We are concerned about tendon ruptures, hypersensitivity reactions, and the influence of the provider's experience and skill on patient safety and efficacy. These safety concerns appear to be adequately addressed in the proposed labeling, REMS, and communication plan. We are not aware of any other safety concerns at this time that would preclude the approval of Xiaflex."

Please let me know if you need anything else for your action package.

Thanks,

Peter

From: Diak, Peter
Sent: Friday, December 04, 2009 3:28 PM
To: Hilfiger, Christopher
Cc: Choi, Lauren Y; Milburn, Cherye; Wheeler, Chris
Subject: RE: PSC

Chris -

Can you clarify if you need something prepared by us. I'm not familiar with this process. For prior approvals, I haven't provided anything for the Action Package. Is this something new?

Peter

From: Hilfiger, Christopher
Sent: Friday, December 04, 2009 3:06 PM
To: Diak, Peter
Subject: RE: PSC

The wrap-up meeting has concluded. We are just trying to get something prepared for the Action Package.

Sincerely,

Christopher Hilfiger

Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3119
Silver Spring, MD 20933-0002

(P) 301.796.4131

From: Diak, Peter
Sent: Friday, December 04, 2009 3:05 PM
To: Choi, Lauren Y; Milburn, Cherye; Wheeler, Chris; Hilfiger, Christopher
Subject: RE: PSC

When is the wrap-up meeting for Xiaflex? I know DAARP is taking action very soon.

My safety concerns are consistent with what has already been presented at the AC and included in the proposed REMS for Xiaflex:

1. Tendon ruptures
2. Anaphylaxis and hypersensitivity reactions
3. Influence of the provider's experience and skills on patient safety and efficacy

Peter

From: Choi, Lauren Y
Sent: Friday, December 04, 2009 2:17 PM
To: Diak, Peter
Subject: FW: PSC

Peter,

Please let us know if you have any safety concerns. Thanks.

LC

From: Hilfiger, Christopher
Sent: Friday, December 04, 2009 10:42 AM
To: Milburn, Cherye; Wheeler, Chris; Choi, Lauren Y
Cc: Adeolu, Abolade
Subject: RE: PSC

<< File: Xiaflex Clinical BLA Review - final 10.5.09.doc >>

Sincerely,

Christopher Hilfiger

Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3119
Silver Spring, MD 20933-0002

(P) 301.796.4131

From: Milburn, Cherye
Sent: Friday, December 04, 2009 9:15 AM
To: Hilfiger, Christopher; Wheeler, Chris; Choi, Lauren Y
Cc: Tossa, Margarita; Adeolu, Abolade

Subject: RE: PSC

You are right Chris as the safety information is presented at the wrap up. As a part of the 21st Century Review process, there really isn't a seperate PSC any longer. The purpose of this part of the meeting is a to tell OSE what kind of safety surveillance will be needed once the product is on the market so our reviewers can watch for any AERs reports indicating problem.

What we will need from you is the MOs final review.

Lauren....let me know if I covered the relavent points.

Cherye

From: Hilfiger, Christopher
Sent: Friday, December 04, 2009 8:31 AM
To: Milburn, Cherye; Wheeler, Chris
Cc: Tossa, Margarita
Subject: FW: PSC

Cherye,

I spoke to Rita Tossa about the Preapproval Safety Conference during the wrap-up meeting for BLA 125338 - Xiaflex. She said that it did not occur at that time. Could you find out if OSE has any safety concerns about approving this product? If there are none I can draft a memo stating that. If there are concern, I suppose the relevant person should write something.

Sincerely,

Christopher Hilfiger

Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3119
Silver Spring, MD 20933-0002

(P) 301.796.4131

From: Ripper, Leah W
Sent: Wednesday, December 02, 2009 5:15 PM
To: Jackson, Colette; Hilfiger, Christopher; Bishai, John
Subject: PSC

Reminder: Don't forget that you have to write up minutes of a Preapproval Safety Conference.

Lee

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

INFORMATION REQUEST LETTER

BLA 125338/0

NOV 2 4 2009

Auxilium Pharmaceuticals, Inc.
40 Valley Stream Parkway
Malvern, PA 19355

Attention: Benjamin J. Del Tito, Jr., PhD
Senior Vice President Quality and Regulatory Affairs

Dear Dr. Del Tito:

Please refer to your Biologics Licensing Application (BLA) 125338, submitted February 27, 2009, under section 351(a) of the Public Health Service Act for Xiaflex (collagenase clostridium histolyticum), for the treatment of advanced Dupuytren's Disease.

We are reviewing your submission and have the following comments, information requests, and notifications of additional requirements. We request a prompt written response in order to continue our evaluation of your application.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

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

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Xiaflex (collagenase clostridium histolyticum) to ensure the benefits of the drug outweigh the risks of tendon rupture and other serious adverse events affecting the injected extremity, and the potential risk of serious hypersensitivity reactions.

Your proposed REMS must include the following:

Medication Guide: As one element of the REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Xiaflex (collagenase clostridium histolyticum) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Xiaflex (collagenase clostridium histolyticum). FDA has determined that Xiaflex (collagenase clostridium histolyticum) is a product that has serious risks (relative to the benefits) of which patients should be made aware because information concerning the risks could

affect patients' decisions to use, or continue to use, Xiaflex (collagenase clostridium histolyticum). Under 21 CFR Part 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are treated with Xiaflex (collagenase clostridium histolyticum).

Communication Plan: We have determined that a communication plan targeted to healthcare providers who are likely to prescribe and administer Xiaflex (collagenase clostridium histolyticum) will support implementation of the elements of your REMS. The communication plan must provide for the dissemination of information about the risks of Xiaflex (collagenase clostridium histolyticum) including tendon ruptures and serious hypersensitivity events (including potential for anaphylaxis), and how to properly inject Xiaflex (collagenase clostridium histolyticum) and perform finger extension procedures.

The communication plan must include, at a minimum, the following:

1. A Dear Healthcare Provider Letter to be distributed at the time of first marketing. This letter should introduce and accompany the educational materials and/or direct healthcare providers how to access the educational materials.

2. Educational materials to instruct healthcare providers how to properly inject Xiaflex (collagenase clostridium histolyticum), perform finger extension procedures, and to inform about the risks of tendon rupture, serious adverse events affecting the injected extremity, and the potential risk of serious hypersensitivity reactions.

3. A description of the intended audience for the communication plan, stating specifically the types and specialties of healthcare providers to which the communication plan will be directed, as well as any professional medical associations and societies that will be sent the communication. The intended audience should include all healthcare providers who are likely to prescribe or administer Xiaflex (collagenase clostridium histolyticum).

4. A schedule for when and how the plan's materials are to be distributed to healthcare providers and medical associations.

Timetable for Assessments: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than annually for years 1 through 5, and at 7 years after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Your proposed REMS submission should include two parts: a "Proposed REMS" and a "REMS Supporting Document." Attached is a template for the Proposed REMS that you should complete with concise, specific information (see Appendix A). Include information in the template that is specific to your proposed REMS for Xiaflex (collagenase clostridium histolyticum). Additionally, all relevant proposed REMS materials including educational and communication materials should be appended to the proposed REMS. Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents as attachments to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

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

The REMS assessment plan should include, but may not be limited to:

1. A narrative summary and analysis of all cases of serious adverse events of the injected extremity, with special attention to tendon ruptures, and all cases of hypersensitivity reactions, including anaphylaxis. For serious adverse events of the injected extremity, the analysis should include a breakdown by healthcare provider specialty, whether the healthcare provider received/participated in education on the risks and proper injection technique, and total number of injections performed. For hypersensitivity reactions, the analysis should include the number and temporal relationship of previous and most recent Xiaflex (collagenase clostridium histolyticum) injections each patient received, the reported signs and symptoms of systemic allergic reactions, including cutaneous, cardiopulmonary, and gastrointestinal manifestations, changes in vital signs, and any pertinent laboratory parameters such as serum tryptase.

   Include your proposed targeted adverse event reporting forms for tendon rupture, and hypersensitivity reactions in the REMS supporting document.

2. A report on the status of healthcare provider education, including the specialty type and number of providers requesting education, the number and percentage of likely providers who received educational materials stratified by educational method (e.g., in person, booklet, DVD, internet), the specialty type and number of providers educated

3. An assessment of the extent of Xiaflex (collagenase clostridium histolyticum) use stratified by
   - indication
   - healthcare provider specialty
   - receipt of education on the risks and proper injection technique (i.e,, the extent to which healthcare providers who have nôt received education are treating patients with Xiaflex (collagenase clostridium histolyticum))

4. An evaluation of the healthcare providers' understanding of proper injection technique and of the serious risk of Xiaflex (collagenase clostridium histolyticum), including the risks of tendon rupture and serious hypersensitivity reactions

5. An evaluation of patients' understanding of the serious risks of Xiaflex (collagenase clostridium histolyticum), including the risks of tendon rupture and serious hypersensitivity reactions

6. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24

7. A report on failures to adhere to Medication Guide distribution and dispensing requirements, and corrective actions taken to address noncompliance

8. Based on information reported, an assessment and conclusion of whether the REMS is meeting its goals, and whether modification to the REMS is needed

Before we can continue our evaluation of this BLA, you will need to submit the proposed REMS.

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend that you use one of the following two statements depending upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- "Dispense the accompanying Medication Guide to each patient." or
- "Dispense the enclosed Medication Guide to each patient."

Prominently identify the proposed REMS submission with the following wording in bold capital letters at the top of the first page of the submission:

BLA 125338
PROPOSED REMS

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 125338
PROPOSED REMS-AMENDMENT

If you do not submit electronically, please send 5 copies of your REMS-related submissions.

If you have any questions, call Christopher Hilfiger, Regulatory Health Project Manager, at (301) 796-4131.

Sincerely,

NOV 24 2009

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

Appendix A: REMS Template

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

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name
Address
Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide or PPI

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

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

B. Communication Plan

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

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

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

C. Elements To Assure Safe Use

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

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

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

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

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

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

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

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

D. Implementation System

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

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

E. Timetable for Submission of Assessments

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

Include the following paragraph in your REMS:

COMPANY will submit REMS Assessments to the FDA <<Insert schedule of assessments: at a minimum, by 18 months, by 3 years and in the 7th year from the date of approval of the REMS.>> To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. COMPANY will submit each assessment so that it will be received by the FDA on or before the due date.

Appendix B: Supporting Document

This REMS Supporting Document should include the following listed sections 1 through 6. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 4 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

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

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # BLA # 125338	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Xiaflex Established/Proper Name: Collagenase Clostridium Histolyticum Dosage Form: injection		Applicant: Auxilium Pharmaceuticals Agent for Applicant (if applicable):
RPM: Christopher Hilfiger		Division: Analgesia, Anastetia, and Rheumatology Products

NDAs:
NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ If no listed drug, check here and explain:

Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.

☐ No changes ☐ Updated
Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

❖ User Fee Goal Date Action Goal Date (if different)	8/29/2009 11/2/09
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ Promotional Materials *(accelerated approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received

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

Application Characteristics [2]	
Review priority: ☐ Standard ☒ Priority Chemical classification (new NDAs only): ☐ Fast Track ☐ Rolling Review ☒ Orphan drug designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: Orphan Status	
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	~~☒~~ Yes ~~☒ No~~
• Press Office notified of action (by OEP)	~~☒~~ Yes ~~☒ No~~
• Indicate what types (if any) of information dissemination are anticipated	~~☒ None~~ ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

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

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☐ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

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

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

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

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

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

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

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

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

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

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

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

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

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

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

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

CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	y
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AP
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	y
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ None
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	

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

• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	y
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	y
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM To be completed ☐ DMEDP ☐ DRISK ☒ DDMAC ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	Filing
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• PeRC *(indicate date of mtg; approvals only)*	☒ Not applicable orphan
• Pre-Approval Safety Conference *(indicate date of mtg; approvals only)*	☐ Not applicable
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 9/15/08
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 8/22/01; 4/4/06

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

• Other (e.g., EOP2a, CMC pilot programs)	
Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	9/16/09
• 48-hour alert or minutes, if available *(do not include transcript)*	y
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None
Division Director Summary Review *(indicate date for each review)*	☐ None
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None
PMR/PMC Development Templates *(indicate total number)*	☐ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	
• Clinical review(s) *(indicate date for each review)*	10/5/09
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	In Clinincal Review
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None 9/28/09
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not needed
❖ Risk Management • REMS Document and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo *(indicate date)* • Review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☐ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None 9/4/09
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None

[5] Filing reviews should be filed with the discipline reviews.

Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 9/2/09
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None 9/18/09
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 9/17/09
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None
• Product quality review(s) *(indicate date for each review)*	☐ None
• ONDQA Biopharmaceutics review *(indicate date for each review)*	
• BLAs only: Facility information review(s) *(indicate dates)*	☐ None
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology *(indicate date of each review)*	☐ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
• BLAs: o TBP-EER	Date completed: ☒ Acceptable 11-10-09 ☐ Withhold recommendation

○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	Date completed: ☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug
Administration
Rockville, MD 20857

IND 5780

Auxilium Pharmaceuticals, Inc.
40 Valley Stream Parkway
Malvern, PA 19355

Attention: Diane P. Myers
Vice President, Quality & Regulatory Affairs, U.S.

Dear Ms. Myers:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AA4500, Clostridial Collagenase for Injection, for the treatment of advanced Dupuytren's disease.

We also refer to the meeting between representatives of your firm and the FDA on September 15, 2008. The purpose of the meeting was to discuss your plans to submit a BLA for AA4500, Clostridial Collagenase for Injection.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at 301-796-2254.

Sincerely,

{See appended electronic signature page}

Sharon Turner-Rinehardt
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Date: April 4, 2006
Time: 3:30 – 5:00 PM
Location: White Oak, Rm 1419
Application: BBIND-5780
Drug Name: AA4500 Clostridial Collagenase
Type of Meeting: "C" Guidance
Meeting Chair: Jeff Siegel, M.D.
Division of Anesthesia, Analgesia and Rheumatology Products, HFD-170

Meeting Recorder: Parinda Jani
Chief, Project Management Staff

Attendees:

Auxilium Pharmaceuticals	**Title**
John Rodzvilla, MD	VP, Medical Affairs
Louise Peacock, BCS,LLB	VP, Regulatory Affairs
Benjamin Del Tito, Jr, PhD	Sr. VP, QA and Regulatory Affairs
Greg Sabatino, BS	Manager, Biotechnology
Jyrki Mattila, MD, PhD	Executive VP, R & D
Uli Schumann, MD	Sr. VP, Clinical Development
Ted Smith, PhD	VP, Biostatistics
Nigel Jones, BS	VP, Clinical Development
Jason Wu, MD, MS	Sr Project Director, Clinical Development
Reid Patterson, PhD, DVM	Toxicologist/Vet
Tu Tu, PharmD, RPh	Manager, Regulatory Affairs
Lawrence Hurst, MD	Consultant
Robert Hotchkiss, MD	Consultant
FDA	**Title**
Bob A. Rappaport, MD	Division Director
Rigoberto Roca, MD	Deputy Division Director
Jeff Siegel MD	Medical Team Leader
Keith Hull, MD, PhD	Medical Officer
Dan Mellon, PhD	Team Leader, Pharmacology/Toxicology
Thomas J. Permutt, PhD	Team Leader, Statistics
David Lee, PhD	Clinical Pharmacology Reviewer
Kim, Yongman, PhD	Statistical Reviewer
Kathy Lee	Product Reviewer
Adam Wasserman, PhD	Pharm/tox Reviewer
Dionne Price, PhD	Statistical reviewer
Henry Startzman, MD	Office of Orphan Products Development
Parinda Jani	Chief, Project Management Staff

BACKGROUND: Purified Clostridial Collagenase for Injection (AA4500) is a parenteral lyophilized product containing two collagenases in an approximately (b) (4) ratio, which are isolated and purified from the fermentation of *Clostridium histolyticum.* AA4500 has been studied in clinical trials for the treatment of diseases such as Dupuytren's contracture, Peyronie's disease, adhesive capsulitis, (b) (4) . The sponsor has been granted an orphan designation for this product, for the treatment of Dupuytren's contracture. Auxilium plans to file a BLA for the use of AA4500 in the treatment of Dupuytren's contracture by mid-2007.

MEETING OBJECTIVES: To introduce the investigational product AA4500, Clostridial Collagenase for Injection, to the Division and to obtain the Division's feedback on the suitability of the clinical development program, including CMC.

DISCUSSION POINTS: Following introductions and opening remarks, the discussion focused on the Sponsor's questions that were included in the March 6, 2006, meeting package. The questions from the meeting package are presented below (bolded text), followed by the Division's responses (italicized text) sent to the sponsor on April 3, 2006. The meeting discussion is presented in normal text.

Question 1:
Based on current clinical experience with Clostridial Collagenase, does FDA concur that Auxilium's proposed Phase 3 study and its open label extension study (Attachment 7), along with the data previously generated by BTC/SUNY at Stony Brook (Attachment 5) will be sufficient to support a BLA submission for AA4500 in treatment of the orphan designated Dupuytren's contracture indication?

FDA's Response to Question 1:
You have proposed a Phase 3 (AUX-CC-851), randomized, double-blind, placebo-controlled, multicenter study with the primary endpoint of a reduction in contracture of the primary joint to within 0°-5° of normal at visit Day 30 following the last injection of up to three injections of AA4500. We note that you have received orphan designation for the proposed indication of Dupuytren's contracture. The Division agrees that if the Phase 3 study shows a positive result, the current clinical experience (including study DUPY-303), the proposed Phase 3 study and the open-label extension will provide sufficient evidence to support a BLA submission for AA4500 in the treatment of Dupuytren's contracture indication.

Meeting Discussion: The sponsor described the design of Studies 851 and 852. Study 851 is a randomized, double-blind, placebo-controlled, multicenter study. During the double-blinded portion of the study, patients would receive a maximum of 3 injections of AA4500. Each injection would be administered 4 to 6 weeks apart, and as needed. Patients would be evaluated at Days 1, 7; 14, and 30 after injection, and the final time point to assess clinical success would be the 30-day post-injection visit. Patients in need of additional treatment after the double-blind period of the study (e.g., incomplete success, other joint/finger involvement) would be given the opportunity to enroll in the open-label study, Study 852. Study 851 is not intended to assess reoccurrence of the disease and would have approximately 144 patients randomized to the active treatment group.

The sponsor has not seen reoccurrence of the contractures in AA4500- treated patients up to 12 months after completion of the treatment. The injection will be allowed to be repeated every 4-6 weeks, not because of reoccurrence is expected, but in the event of failure to respond to the previous injection.

The Division stated that, for patients who require multiple injections of multiple joints, treatment exposure would be more comparable to chronic therapy than to acute therapy. Ours concerns relate to hypersensitivity reactions and the safety of multiple injections. The Division recommended that the sponsor evaluate all treated patients by enrolling them into the open-label study to more thoroughly assess safety over one year. One specific question such a study may confirm is whether reoccurrences are observed over the course of one year.

There was discussion about the amount of safety data to be submitted with the original application. The sponsor would prefer to submit 12-month safety data from Study 851 and 9-month safety data from Study 852 at the time of submission, and additional safety data from Study 852 with the 120-day safety update.

The Division stated that all the data intended to support the application should be included at the time of submission. Therefore, the 12-month safety data from both studies should be included with the original application.

Question 2:
Does FDA agree with or have comments on the current study design as specified in the draft Protocol of Auxilium's Phase 3 study (AUX-CC-851) provided in Attachment 6 to demonstrate the safety and efficacy of AA4500 in treatment of Duptuytren's contracture?

FDA's Response to Question 2:
In general terms, the design of the Phase 3 study AUX-CC-851 appears acceptable. In the final protocol, we recommend you include a method for imputation of missing data for the primary endpoint. An acceptable imputation technique that would not overestimate the proportion of responders would be a non-responder imputation method. We also recommend that you rank the secondary endpoints. For the open-label extension study, we note that to reach conclusions about the durability of response following AA4500 injection, it will be important to have only very small amounts of missing data.

Meeting Discussion: The Division questioned how the missing data for the primary endpoint would be handled. Given that the sponsor expects to have very little missing data, the primary endpoint would be defined as a success at any visit following injection (i.e., Days 1, 7, 14, and 30); and as reoccurrence of contracture does not appear to be an issue, the sponsor intends to use LOCF for imputation of missing data.

The Division stated that an LOCF imputation strategy for missing data for the primary analysis will be acceptable and that a non-responder imputation method could be used as a sensitivity analysis. Since there are no plans for a durability claim, the sponsor's proposal not to include an imputation method for reoccurrence is acceptable; however, the Division also noted that, if they changed their mind after the data had been analyzed, a retrospective attempt to establish the validity of a claim may encounter difficulties if the endpoints and analyses were not pre-

specified. The Division suggested that the sponsor define the endpoints and statistical analysis plans prospectively.

Question 3:
Does FDA agree that the 35 subjects from previous Phase 3 study DUPY-303 can be used in conjunction with Auxilium's proposed Phase 3 program to evaluate safety and efficacy of AA4500?

FDA's Response to Question 3:
For licensure of AA4500, you will need to provide substantial evidence of efficacy, which usually consists of at least 2 adequate and controlled trials. The Division agrees that on its face, there does not appear to be any reason why study DUPY-303 could not be used as one of two trials demonstrating efficacy of AA4500.

There was no further discussion necessary.

Question 4:
Does FDA agree that the participation of a minimum al 10 investigator sites in the proposed Phase 3 pivotal study (AUX-CC-851) is sufficient to demonstrate reproducibility of results across practitioners?

FDA's Response to Question 4:
Yes, the Division agrees that the participation of at least 10 investigator sites in the proposed Phase 3 study (AUX-CC-851) is sufficient to demonstrate reproducibility across practitioners. However, it will be important that each study site enroll adequate numbers of patients to assess responses across centers.

There was no further discussion necessary.

Question 5:
In light of the existing clinical data, does FDA believe that Auxilium's plan to file a BLA for AA4500 with the efficacy results from the Phase 3 study and 6 months post-first injection follow-up for subjects in the acute Phase 3 study is acceptable?

FDA's Response to Question 5:
You have limited data on the number of patients who will require re-injection over the course of a year following a course of treatment with AA4500. Given the lack of data, it is possible that some patients will require multiple injections over the course of a year. Therefore, 6-month data may not adequately assess the safety of AA4500. For this reason, data on 12-month follow-up in the open-label extension trial will be required at the time of BLA submission. You will need to revise the open-label extension study to characterize safety and efficacy over 12 months. The revised open-label extension trial should enroll all patients from study AUX-CC-851. The revised protocol should characterize the durability of response (i.e., percent with recurrence and time to recurrence using a prespecified definition of recurrence of contracture) of each injected joint over this 12-month time frame and specify when and in what manner recurrent contractures would be retreated.

Meeting Discussion: See discussion under Question 1.

Question 6:
Based on the analytical comparability data provided in the CMC overview (Attachment 8) for the material produced from the optimized manufacturing process (Process 2), does FDA concur that Auxilium's Collagenase from Process 2 is comparable to Collagenase from Process 1?

FDA's Response to Question 6:
Yes, however we have the following comments:

1. *Provide the bioburden testing plan for the drug substance manufactured by Process 2 and Process 3.*

2. *The drug substance stability plan for the Process 3 material includes time points 4.5 months and 15 months. These time points are not required, however, please add a 9 month time point. For further guidance see ICH Guideline Q1A(R2) "Stability Testing of New Drug Substances and Products" or Q5C "Stability Testing of Biotechnology/Biological Products."*

3. *Optimize your peptide mapping assay to be able* (b) (4)

4. *Add particulate testing to your drug product release testing protocols.*

5. *Indicate which assays are stability-indicating.*

6. *What are the double peaks for AUX-I and AUX-II seen in the* (b) (4) *assay? Does the distribution of the double peaks change over time (i.e. is this assay stability-indicating)?*

7. (b) (4)

8. *Provide a description of the preparation of the* (b) (4) *including storage conditions and the number of vials created.*

9. *Provide information on the reference standards used for the drug substance and drug product. If you do not have reference standards, please develop them.*

Meeting Discussion: The Division asked the sponsor to submit the immunogenicity assay for review as soon as possible. The Division wants to make sure that the assay is sensitive enough and will provide comments within a reasonable timeframe. The sponsor asked for clarification regarding the request to add particulate testing to the product-release testing protocols. The sponsor's understanding is that under USP, since the product is going to be injected into joints, they were exempted from this test. Ms. Lee will follow-up on this point and will provide a response.

Question 7:
Does FDA concur that Auxilium's strategy, as provided in the Non- clinical overview (Attachment 9) to demonstrate the pre-clinical comparability of materials produced by the optimized processes, is acceptable?

FDA's Response to Question 7:
Overall your proposal appears to be acceptable assuming you demonstrate comparability on the basis of biochemical and biological characterization (i.e., identity, purity, stability, and potency). However, the histopathology results from the two comparability bridging studies should also be evaluated prior to initiating clinical dosing in the Phase 3 study.

Meeting Discussion: The sponsor asked whether the Division wanted the sponsor to evaluate the report internally or to submit it to the Agency for review prior to starting the study. Dr. Mellon stated that histopathology data should be submitted to the Agency prior to initiating the Phase 3 study. The sponsor stated that the Phase 3 trials will be conducted with the new formulation (Process 2 formulation) and the new Process 3 formulation should be completed and ready for the Phase 3 trial in July 2006. Ms. Lee stated that the CMC data will be required prior to the clinical shift and that the Division needs to approve the use of the new formulation for the Phase 3 study. Ms. Lee also recommended that Auxillium begin the Phase 3 trial with the Process 3 material.

The preclinical bridging program for the new formulation is going to be dependent on the CMC comparability of the two formulations. The Division may have further issues to discuss with the sponsor if the formulations are not considered adequately comparable. The sponsor may submit preclinical data as they become available. The Division prefers final reports, but is willing to accept audited drafts that contain full histopathology, complete line-listings, and signed pathology reports.

Question 8:
According to minutes from the EOP2 meeting held on August 22, 2001 (Attachment 11), FDA advised that due to the nature of the product and its intended use for the acute treatment of Dupuytren's contracture, chronic toxicity, reproductive toxicity, and carcinogenicity studies are not required to support a BLA. Is Auxilium correct in assuming that this advice remains valid?

FDA's Response to Question 8:
The FDA's previous advice regarding the lack of a need for chronic toxicity and carcinogenicity study remains valid. Reproductive toxicology studies will also not be necessary assuming that systemic exposure to the drug substance is not detectable.

Meeting Discussion: The systemic exposure data will be required in order to determine whether the listed preclinical studies will be required or not, and what information would be appropriate to include in the label.

Additional Discussion: The Division stated that there were no data on systemic exposure submitted in the application. The sponsor stated that they had evaluated four patients for systemic exposure and there was no collagenase found in serum and only fragments were found in urine.

The Division suggested that the sponsor submit a proposal on how they intend to evaluate the clinical pharmacology data. If appropriate, they may request a bio-waiver based on the results of this evaluation. It will be acceptable to obtain data in a subset of Study 851 patients. The proposed assay should be very sensitive and specific. The sponsor can submit the proposal and the Division will provide comments within a reasonable timeframe.

The sponsor inquired whether they could not conduct nonclinical reproductive toxicity studies and categorically accept a Pregnancy "C" Category designation, should there be evidence of human systemic exposure to A4500. The sponsor was informed this was not an option and that reproductive toxicity studies would need to be performed to establish the appropriate category designation.

There was extensive discussion regarding the number of patients to be included in the safety database. The Division stated that, even though this product has Orphan Drug designation for the treatment of Dupuytren's contracture, safety data should be collected in accordance with the ICH requirements for a New Molecular Entity (NME). The sponsor could enroll more patients in the open label study and collect data for at least 1,000 patients.

The sponsor stated that the safety database will have data from studies in other indications and will have data from approximately 500 – 600 exposures. They have not seen any Adverse Events related to systemic exposure.

The Division responded that the sponsor needs to try to recruit additional patients. The Division is willing to review a proposal for the number of patients to be included in the safety database including the addition of patients treated with AA4500 for other disorders, e.g., Peyronie's disease. The proposal should include a rationale supported by data, and documentation of due diligence and any additional measures that the sponsor might have taken to recruit additional patients.

DECISIONS (AGREEMENTS) REACHED:

1. The BLA will be complete at the time of submission.
2. The sponsor will submit an immunogenecity assay for the Division's review. Comments will be provided within a reasonable time frame. Results of the immunogenecity assessment from the clinical trials must be submitted with the original application.
3. The sponsor will submit plans for assessing systemic exposure of this product. Comments will be provided within a reasonable time frame. If there is any systemic exposure, additional pharm/tox studies may be necessary.
4. The sponsor will submit a rationale as to why a smaller safety database should be adequate for this product.
5. The Division will follow-up on the requirements of particulate testing.
6. Complete histopathology study reports will be submitted to the Agency prior to initiation of Phase 3 study.
7. The labeling will be constructed in the new PLR format.

Post-meeting note: After discussion with the Deputy Director of the Division of Therapeutic Proteins (Dr. Barry Cherney), it was determined that we will require particulate testing for the release of the drug product.

Linked Applications	Sponsor Name	Drug Name
'ND 5780	HURST LAWRENCE C MD	Collagenase (C. histolyticum, Advance Biofactures)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PARINDA JANI
05/12/2006

MEETING MINUTES

Meeting Date: September 15, 2008
Location: CDER White Oak, Conference Room 1309, Building 22, Via Teleconference
IND/Name: AA4500, Clostridial Collagenase
Indication: Treatment of advanced Dupuytren's disease
Sponsor: Auxilium Pharmaceuticals
Type of Meeting: Type B, Pre-BLA
Meeting Chair: Sarah Okada, M.D., Division of Anesthesia, Analgesia and Rheumatology Products, HFD-170
Minutes Recorder: Diana Walker, RPM

BACKGROUND: Clostridial Collagenase consists of two microbial collagenases, Collagenase AUX-I and AUX-II. The collagenases are secreted bacterial proteins isolated from Clostridium histolyticum. AUX-I is a single polypeptide chain consisting of (b) (4) amino acids and AUX-II is also a single polypeptide changing consisting of (b) (4) amino acids. Auxilium intends to develop AA4500, Clostridial Collagenase for the treatment of Dupuytren's disease.

Auxilium Attendees	
Name	**Title**
Anthony DelConte, M.D.	Chief Medical Officer
Ben Del Tito, Jr., Ph.D.	Sr. VP, Quality & Regulatory Affairs
Susan Emeigh Hart, VMD, Ph.D.	Sr. Director, Pre-Clinical Development
Louise Peacock, BSc, LLB	VP, Regulatory Affairs – International
John Rodzvillla, M.D.	VP, Medical Development
Wayne Herber, Ph.D.	VP, Process Development
Ted Smith, Ph.D.	VP, Biometrics
Tu Tu, Pharm.D.	Sr. Manager, Regulatory Affairs
Diane P. Myers	VP, Quality & Regulatory Affairs, U.S.
Lauren Tornetta, MS, MBA	Manager, Regulatory Affairs

FDA Attendees	
Name	**Title**
Rigoberto Roca, M.D.	Deputy Director, Division of Anesthesia, Analgesia and Rheumatology Products
Sarah Okada, M.D.	Clinical Team Leader
Kathleen Coyle, M.D.	Medical Officer
Jeffrey Siegel, M.D.	Clinical Team Leader
Srikanth Nallani, Ph.D.	Clinical Pharmacology Reviewer
Dan Mellon, Ph.D.	Pharmacology Toxicology Supervisor
Asoke Mukherjee, Ph.D.	Pharmacology Toxicology Reviewer
Ashutosh Rao, Ph.D.	Biologist, Division of Therapeutic Proteins (DTP)
Kathy Lee, M.S.	Acting Associate Lab Chief, Lab of Biochemistry, DTP
Emily Shacter, Ph.D.	Lab Chief, Lab of Biochemistry, DTP
Huiqing Hao, Ph.D.	Pharmacology Toxicology Reviewer
Jonathan Norton, Ph.D.	Statistics Reviewer
Sharon Turner-Rinehardt	Regulatory Health Project Manager
Diana Walker, Ph.D.	Regulatory Project Manager
Jessica Benjamin	Regulatory Project Manager

GENERAL DISCUSSION:

Following introductions, the meeting focused on the responses to the questions included in the May 12, 2008, meeting package for IND 5780. The Sponsor accepted the Division responses to questions 1, 3, 5, 6, 7 (except ii), 8, 9, 10, 11, 12, 13, 14 (except v), 15 and the additional comments (except 1 and 2). The Sponsor requested that the discussion focus on the following questions: 2, 4, 7ii, 14v, 16, and additional comments 1 and 2. The questions are presented below in *italicized* text. The Division's responses, prepared prior to the meeting and sent to the Sponsor via email on September 11, 2008, are **bolded**. Discussion is presented in normal text. The meeting was conducted via teleconference.

AGENDA QUESTIONS from SPONSOR and FDA COMMENTS

Question 1. The proposed Drug Substance (DS) specification is provided in Section 5. Does the Division agree that this is an appropriate specification for release of DS?

FDA Response

A final determination of acceptable release testing and specifications will result from the complete review of the BLA, and all data available at that time will be used to make that determination. Specifications should be justified in the BLA application based on manufacturing history, process capability, and nonclinical and clinical experience of the relevant lots. In the BLA, provide detailed descriptions of the meaning of "comparable to reference standard" for the SDS-PAGE and RP-HPLC assays.

Discussion: There was no further discussion on this question.

Question 2. The proposed Drug Product (DP) and Sterile Diluent specifications are provided in Section 5. Does the Division agree that these are appropriate specifications for release of DP and Sterile Diluent?

FDA Response
A final determination of acceptable release testing and specifications will result from the complete review of the BLA, and all data available at that time will be used to make that determination. Specifications should be justified in the BLA application based on manufacturing history, process capability, and preclinical and clinical experience of relevant lots. In the BLA, provide a detailed description of the meaning of "comparable to reference standard" for the SDS-PAGE and RP-HPLC assays. Additionally, you will need to test for sub-visible particles that range in size from (b) (4) both at release and on stability.

Discussion: The Sponsor requested that the Division provide a rationale for requiring testing for sub-visible particles. The Division stated their concern with the impact of sub-visible particles on immunogenicity, and that the current policy is that all products are required to undergo testing for sub-visible particles. Tracking changes in sub-visible particles throughout the production process over time is important for comparison and detection of potential changes in immunogenicity of the drug product. The Sponsor was referred to the position paper published in the Journal of Pharmaceutical Science. It was also confirmed that sub-visible particle test specifications should be justified in the BLA submission based on manufacturing history, process capability, and the preclinical and clinical experience of the relevant lots. The Sponsor asked for clarification that testing was required for drug product only and the Division found this acceptable.

Question 3. Does the Division agree that the potency specification and limits for control of the DS and DP are justified based on the information provided in Section 5?

FDA Response
Yes, the specifications are acceptable. You will need to have a well-controlled reference standard produced in the same manner as the lots that are tested.

Discussion: There was no further discussion on this question.

Question 4. Does the Division agree with the host-cell protein assay approach provided in Section 5?

FDA Response
Yes, the host-cell protein assay approach is acceptable. You should validate the new ELISA test with a Western blot analysis.

Discussion: The Sponsor asked the Division to clarify whether the polyclonal anti-serum should be used to validate the new ELISA test via Western blot analysis. The Division found this acceptable.

Question 5. Process validation for the AA4500 bulk DS manufacturing process is currently being completed. The remaining studies are being conducted using qualified scale-down models for the (b) (4)

FDA Response

Yes, the approach appears reasonable. It appears that you will be submitting parts of the BLA as a Quality by Design (QbD) approach. Participation in the Office of Biotechnology Product's pilot program on QbD is encouraged (FR notice, Docket No. FDA–2008–N–0355).

Discussion: There was no further discussion on this question.

Question 6. At the time of the BLA filing Auxilium plans to submit 24 months of DP stability data from one development lot, 18 months of stability data from three development stability lots, and 12 months of stability data from four commercial scale development stability lots. See Table 11, Table 12, Table 13, Table 14, and Table 15 in Section 5 for details.

Additionally at the time of the BLA filing, Auxilium plans to submit 24 months of Sterile Diluent stability data from two development lots and 18 months of stability data from four lots (one development lot and three commercial scale lots). See Table 16 and Table 17 in Section 5 for details.

In addition, Auxilium will amend the original BLA application at approximately 4 months post-submission with additional stability data for both AA4500 DP and Sterile Diluent in order to provide data that will further support a 24-month expiration date for both AA4500 DP and Sterile Diluent. The purpose of this submission would be to provide up to 24 months of data for DP lots FIN-0355, FIN-0358 and FIN-0366 and up to 24 months of data for Sterile Diluent lots FIN-0322, 7206 and 7212.
Does the Division agree with this approach to obtain 24 months expiry dating at approval?

FDA Response

The plan appears to be acceptable. You will need to submit trend analysis on the stability data, e.g., confidence interval trending. 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. You will also need to provide shipping validation studies, photostability studies, and leachable and extractables data for the container closure

systems used for the drug substance (DS) and drug product (DP). You will also need to provide post-approval DS and DP stability protocols for the lots that will be placed on annual stability.

Discussion: There was no further discussion on this question.

Question 7. Based on the summary of all nonclinical studies to be included with the BLA (Table 18), the human safety database that will be available from the clinical trial program (Section 7.8), and previous agreements with the Agency (22Aug2001 EOP2 and 04Apr2006 Type C meetings), please confirm that the nonclinical package is sufficient to support a BLA submission for AA4500 for the treatment of advanced Dupuytren's disease:

Specific questions:

i. *In addition to the GLP nonclinical studies conducted by Auxilium with AA4500, nonclinical information in support of AA4500 has been derived from the published literature and non-GLP studies performed with AA4500 (early BTC process) that were submitted as part of the original IND. Does the Division agree that the information derived from the literature and from BTC studies can be used to supplement the GLP studies conducted by Auxilium in support of the BLA for AA4500 for treatment of advanced Dupuytren's disease?*

FDA Response

The non-GLP studies performed with AA4500 via the early BTC process can be submitted to support the definitive GLP studies intended to support the BLA for AA4500 for the treatment of advanced Dupuytren's disease.

The Division notes that your GLP toxicology study in the dog does not demonstrate a clear NOAEL. In the absence of a clear NOAEL, your BLA submission should include rationale for why the histological findings in the dog do not raise safety concerns for your drug product.

Final determination of the adequacy of the existing nonclinical toxicology studies can only be provided once a final determination of the comparability of the nonclinical batches to the clinical formulation is made (see response to part ii below).

Discussion: There was no further discussion on this question.

ii. *As per the IND submissions dated 18Sep2006 and 06Dec2007, and the subsequent Agency letter received on 27May2008 (See Attachment 3), it is our understanding that comparability of product made by BTC Process 1,* (b) (4) *Process 3, and*

Auxilium-Horsham Process 3 has been demonstrated. Does this Division concur with this assessment?

FDA Response

Until the following data are provided, we are unable to determine if the DS produced by Horsham Process 3 and the DS produced by (b) (4) Process 3 are comparable:

1. **Provide a rational for the shift in the retention times for the Horsham DS, AUX I and AUX II intermediate lots in the SEC-HPLC and RP-HPLC assays relative to the lots produced at (b) (4)**

2. **It appears that you have used two different gel types for SDS-PAGE assay. The (b) (4) samples were run on an (b) (4) and the Horsham samples were run on another type of gel (unknown). Additionally, the protein loading appears to be different. Provide information on the gel type and protein loading concentration. Provide evidence that the data generated are comparable. If the data are not comparable; please perform SDS-PAGE for the DS on the same gel using the same loading concentration.**

In addition, we have the following comments on the additional characterization testing you have performed for the Horsham and (b) (4) lots.

1. **The amino acid analysis data cannot be compared as presented. Please present the amino acid analysis results for the Horsham and (b) (4) lots using the same calculations to allow for meaningful comparison of the data.**

2. **The chromatograms from the (b) (4) sequencing appear to be dissimilar. The data are presented on different scales, with variable peak heights and a variable number of peaks. Provide an explanation for the difference in the chromatograms and provide a rationale for why you think they are similar.**

Your BLA submission should contain a summary table outlining the impurity specifications in all nonclinical and clinical batches in order to document the applicability of the nonclinical studies conducted to support your proposed clinical studies.

If comparability is not demonstrated, your BLA submission must include a 3-month repeat-dose toxicology study with the clinical formulation that demonstrates a clear NOAEL and evidence of complete reversibility of the histopathological changes.

Discussion: The Sponsor outlined their approach to the analytical comparability using the Horsham and (b) (4) processes, and referenced examples within the IND submission. The Division stated that it was not clear during the review that a (b) (4) reference standard had been used and asked if that particular lot had been used as a (b) (4) reference standard in the toxicology studies. The Sponsor stated that the (b) (4) standard had been used in studies (b) (4) 520, (b) (4) 00006 and (b) (4) 1007-1671.

The Sponsor stated that the shift in the retention times for the Horsham DS, AUX I and AUX II intermediate lots in the SEC-HPLC and RP-HPLC assays relative to the lots produced at (b) (4) (b) (4)

The Sponsor stated that the (b) (4) lots were analyzed using (b) (4) SDS-PAGE gels, whereas the Horsham lots were analyzed using (b) (4) gels. After discussion of the SDS-PAGE gel optimization methods employed by the Sponsor, the Division agreed that while some examples of drug product characterization appeared to be comparable, there were concerns with the drug substance characterization. The Division advised the Sponsor that resolving power appeared to be lost when they used the (b) (4) method, and would like to see greater resolution during future development. The Division further advised that SDS-PAGE is not, and should not be used as, a true identity test. The Sponsor agreed with this assessment.

The Sponsor agreed that the amino acid analysis, as presented, is not comparable and will provide data using the same calculation method to show comparability.

The Sponsor stated that when the Division assesses the mass spectrometry data, the qualitative data and tables should be used for comparison, but not the spectra data. The Division disagreed, and stated that the spectra data submitted can be used for comparison. However, the Sponsor should resubmit their rationale regarding the use of spectra data to assess comparability.

The Sponsor requested permission to provide additional data to address concerns regarding analytical comparability for SEC-HPLC, RP-HPLC, SDS-PAGE, and amino acid analysis, and asked if this could be submitted with the BLA. The Division stated that the Sponsor should provide detailed tables including, but not limited to, lot numbers, specific studies, and comparability data with the submission; however, this data must be submitted prior to the BLA submission.

The Sponsor stated that they do not plan to conduct any further nonclinical bridging studies. The Division agreed on the condition that the Sponsor provides clear evidence prior to the BLA submission that previous toxicology studies are sufficient, and that the drug product comparability concerns have been addressed. The Division emphasized that the Sponsor must provide a table containing the lot numbers used during the studies to facilitate a review of comparability. The Sponsor agreed and will provide analytical profiles prior to the BLA submission.

iii. *The Division previously advised that reproductive toxicology studies would not be necessary assuming that systemic exposure to the DS is not detectable (04Apr2006 Type C Meeting). Due to the lack of systemic exposure detected in Dupuytren's subjects in Study AUX-CC-855, no additional reproductive toxicity studies are proposed. Furthermore, no further safety pharmacology or Absorption, Distribution, Metabolism, and Excretion (ADME) studies are proposed for the same reason. Does the Division agree with this position?*

FDA Response

Based on the information submitted to date documenting the lack of systemic exposure to AA4500, further reproduction and developmental toxicology studies will not be required.

Your BLA submission should address the potential for general and reproductive and developmental toxicity, if anti-product antibodies form which cross react with self-antigens. This must include a discussion of the potential for anti-product antibodies to bind to and neutralize endogenous collagenase.

Discussion: There was no further discussion on this question.

Question 8. Based on the summary of all clinical studies to be included with the BLA (Table 25), does the Division agree that the proposed clinical package provides sufficient evidence of efficacy to support a BLA submission for AA4500 for the treatment of advanced Dupuytren's disease? Results of primary efficacy endpoints from three, randomized, double-blind, placebo controlled studies (DUPY-303, AUX-CC-857, and AUX-CC-859) will be included in the BLA submission. Additional clinical efficacy data including secondary endpoints at the proposed dose to support the claims of efficacy will also be included.

FDA Response

Your proposed BLA submission will include data collected from 409 subjects who received up to three injections of AA4500 (0.58 mg) into a primary joint in three double-blind placebo-controlled studies: DUPY-303, AUX-CC-857 and AUX-CC-859. These three studies reportedly met the primary endpoint of a higher proportion of patients achieving contracture reduction to within 5 degree of normal at a pre-identified target joint compared with placebo, 30 days after the last injection of study drug. Supportive efficacy

data will include results from three ongoing open-label Phase 3 clinical studies with over 890 subjects who have received approximately 1600 injections in these studies.

The proposed safety database for the BLA submission will include data from the three controlled studies and their long-term extensions, and supportive data from the remaining 6 studies in the clinical development program, comprising greater than 1000 subjects treated for advanced Dupuytren's disease who have received at least one injection at the proposed dose. In total, these patients have received over 2500 injections of AA4500. These safety data will also include over 100 subjects who have been followed for 12 months following their first AA4500 injection.

Your proposals are consistent with expectations previously set forth in your previous discussions with the Division and are adequate to support a BLA submission for AA4500 for the treatment of advanced Dupuytren's contractures.

Discussion: There was no further discussion on this question.

Question 9. A human pharmacokinetic study of AA4500 (AUX-CC-855) has been completed in Dupuytren's subjects with results showing that levels of AUX-I and AUX-II were below the detectable limit of the validated analytical methods in all plasma samples and for all time points evaluated (from 5 mins to 24 hrs following the 0.58-mg injection of AA4500 into a Dupuytren's cord). The lower limit of quantitation for the validated methods is 5 ng/mL for AUX-I and 25 ng/mL for AUX-II. This pharmacokinetic study confirmed the lack of systemic exposure with intralesional administration of AA4500 in a clinical setting. Does the Division concur with the assessment that these results demonstrate a lack of systemic exposure with intralesional administration of AA4500?

FDA Response

We concur that the described results of AUX-CC-855 submitted in the briefing package appear to demonstrate a lack of systemic exposure with intralesional administration of 0.58 mg AA4500.

Discussion: There was no further discussion on this question.

Question 10. Serum samples have been collected during the Phase 3 clinical program for AA4500 for the treatment of advanced Dupuytren's disease and stored for immunogenicity analyses. Antibody testing on all samples will be batched and results of the immunogenicity assessment (total immunoglobulins) from the clinical trials will be submitted in the BLA application. Confirmed positive human serum antibody samples are being collected and stored for the purpose of determining whether these human anti-Clostridial collagenase antibodies are neutralizing, but best efforts to further develop/validate the method are ongoing. We plan to be prepared for a discussion with the Division surrounding these method development efforts and

the clinical relevance of measuring neutralizing antibodies for this program at the Pre-BLA meeting.

FDA Response

You will not need to develop a neutralization assay prior to submitting the BLA. You will need to continue your efforts to develop an assay to determine if the anti-AUX I and anti-AUX II antibodies are neutralizing. If you are unable to develop a neutralization assay(s) with (b) (4), you should consider adapting your potency assays for this purpose.

Discussion: There was no further discussion on this question.

Question 11. The safety database for AA4500 proposed for inclusion in the BLA will contain safety data from more than 1000 subjects treated with AA4500 for advanced Dupuytren's disease, including >100 subjects followed for at least 1 year. These data are in-line with the

Agency requirements for safety as specified at the 04Apr2006 Type C meeting. Does the Division concur that the proposed safety database will provide sufficient exposure data to support safety in the BLA submission for the proposed indication?

FDA Response
See answer to Question 8.

Note that the BLA should also include your proposals for managing potential safety concerns that may not have been demonstrated in clinical trials, such as the possibility of anti-product antibodies that are cross-reactive with endogenous collagenase (especially if these antibodies could cross the placenta during fetal development), how you propose to ensure proper administration of AA4500 by providers if approved, and how you propose to assess for the incidence of post-marketing events of tendon rupture in order to determine whether the incidence is higher than that noted in the clinical trials.

Discussion: There was no further discussion on this question.

Question 12. As per MAPP 6020.3 "Priority Review is granted if the drug product, if approved, has the potential to provide, in the treatment, prevention, or diagnosis of the disease, one of the following: (1) safe and effective therapy where no satisfactory alternative therapy exists; or (2) a significant improvement compared to marketed products."
Auxilium believes that the BLA application for AA4500, Clostridial collagenase for Injection, is eligible for Priority Review because it meets the above definition as detailed below:

- *No medical treatment (i.e., FDA approved drug product) is currently available for Dupuytren's disease, which is a debilitating condition.*

- *Orphan Designation was granted as amended (23May1996) for advanced Dupuytren's disease which the Agency defined as involutional or residual phase of Dupuytren's disease.*
    - *Advanced Dupuytren's disease is a condition (contracture) that occurs in the involutional and residual phase of the disease (ref Tubiana, et al., 2000. page 82-83, McFarlane, 1990. page 26-30).*

Does the Division concur that the BLA application will be granted Priority Review once it is submitted and accepted for filing?

FDA Response
It is likely that the application will be granted priority review but determination will be made upon submission of the BLA.

Discussion: There was no further discussion on this question.

Question 13. The dossier for the AA4500 BLA will be provided electronically in the Common Technical Document (eCTD) format. Please see our proposed outline of the Table of Contents for eCTD (see Attachment 10). Does the Division concur with our approach?

FDA Response
In general, your approach appears acceptable. Refer to *http://www.fda.gov/cder/regulatory/ersr/ectd.htm* for the most recent information on eCTD specifications.

Discussion: There was no further discussion on this question.

Question 14. Does the Division concur with the information described below?

i. Auxilium intends to submit the BLA for AA4500, Clostridial collagenase for Injection, in an eCTD format. The electronic submission will be prepared in accordance with the ICH eCTD Specifications version 3.2, dated February 04, 2004, and the following FDA Specifications: eCTD Backbone Files Specification for Module 1, version 1.3, dated December 13, 2006; eCTD Backbone Files Specification for Modules 2 through 5, version 1.1, dated March 11, 2004; eCTD Backbone Files Specifications for Study Tagging Files (STF), version 2.6, dated July 25, 2005; eCTD Table of Contents Headings and Hierarchy, version 1.2, dated July 06, 2005; and Study Data Specifications, version 1.3, dated November 27, 2006.

FDA Response
You should contact *esub@fda.hhs.gov* with this question and with your eCTD submission plans.

Discussion: There was no further discussion on this question.

ii. The eCTD BLA for AA4500 will be generated by (b) (4) *who has successfully submitted a pilot eCTD submission (reference eCTD pilot 90024; June 2004). On this basis, Auxilium requests a waiver for the requirement to submit a pilot eCTD submission.*

FDA Response
See response to Question 14.i.

Discussion: There was no further discussion on this question.

iii. Paper archival copies will be provided only for those items with original signature (cover letter, Form FDA 356h and Items 13-18). These documents will be submitted electronically as well.

FDA Response

This is acceptable.

Discussion: There was no further discussion on this question.

iv. *The proposed labeling with this application will be provided in both Structured Product Labeling (SPL) and in Microsoft WORD format in accordance with PLR. All additional labeling components (e.g., carton, containers, etc.) will be provided as PDF files.*

FDA Response
This is acceptable.

Discussion: There was no further discussion on this question.

v. *With the submission of the datasets, individual subject listings (Appendix 16.4) will not be included with the Clinical Study Reports (CSRs). Similarly, subject Case Report Forms (CRFs) (Appendix 16.3) and Subject Data Listing (Appendix 16.2) will be provided separately and not appended to the CSRs.*

FDA Response
If you are referring to providing the link to these individual subject listings and CRFs separate in the electronic table of contents, and not in the CSR file itself, this is acceptable.

Discussion: The Sponsor requested clarification that it is acceptable to submit individual subject listings as SDTM (Study Data Tabulation Model) datasets in CDISC (Clinical Data International Standards Consortium). The Division stated that this seems acceptable but that final confirmation of this would be provided as a post-meeting note.

Post Meeting Note: Your proposal to submit individual subject listings as SDTM datasets in CDISC is acceptable.

vi. *A STF will be provided for each study report, which will identify all the components of the study report, including all associated CRFs and datasets. The STF will allow navigation to these components.*

FDA Response
This is acceptable.

Discussion: There was no further discussion on this question.

vii. SAS datasets will be provided in lieu of case report tabulations in accordance with the 1999 FDA Guidances, "Providing Regulatory Submissions in Electronic Format – General Considerations," and "Providing Regulatory Submissions in Electronic Format – NDAs". Separate subject profiles, in PDF format, are not planned to be submitted. Each dataset will be provided as a SAS transport file in accordance with the above referenced guidance. Both raw and analysis datasets will be provided.

FDA Response
This is acceptable.

Discussion: There was no further discussion on this question.

viii. The raw datasets will be modeled in accordance with the CDISC Study Data Tabulation Model Implementation Guide: Human Clinical Trials v1.01, which comprises version 3.2 of the Submission Data Standards.

FDA Response
This is acceptable. Refer to http://www.cdisc.org/models/sdtm/v1.1/index.html for the most recent version of the Implementation Guide.

Discussion: There was no further discussion on this question.

ix. For scanned CRFs, all CRFs will be provided as PDF files, organized by study, site and subject. They will be bookmarked by visit and domain, as well as provide a hypertext link from all data clarification forms to the corrected page.

FDA Response
This is acceptable.

Discussion: There was no further discussion on this question.

x. Auxilium intends to provide a clinical summary in Module 2 which incorporates all elements of ISS and ISE as well as providing complete ISS and ISE documents in Module 5. This is intended to fulfill the requirements of efficacy and safety for the US.

FDA Response
This is acceptable.

Discussion: There was no further discussion on this question.

Question 15. Does the Division agree AA4500 will qualify for a pediatric exemption/waiver for pediatric development and use on the basis that Dupuytren's disease affects mainly those aged 45 and older and therefore, is not likely to be used in a substantial number of pediatric subjects? Dupuytren's disease is a disease of the adult population (Welsh and Spencer, 1990 and Leclerq, 2000). Although there have been reported cases of the disease occurring in ages less than 18 years of age, the scarcity of reported cases confirm the fact that Dupuytren's disease in children is a rarity (Marsh and Kelly, 2008 and Cheryl, et al., 1991). A survey of the population of men and women in Lancashire, England was performed in 1962 and found an incidence of 0.10 % in men 15 -24 years of age (Welsh and Spencer, 1990). Another study identified only 3 pediatric cases of Dupuytren's disease in a 25-year period (Cheryl, et al., 1991). Since 1832, there have been only seven published cases of histologically proven Dupuytren's disease in children under 10 years of age (Marsh and Kelly, 2008).

The rarity of Dupuytren's disease in children is what precludes the clinical study of AA4500 (Clostridial collagenase for injection) in children. There would be practically no demand for the use in children and there would be no achievable way to enroll an adequate number of children to conduct and complete a clinical trial in a reasonable time period. Therefore Auxilium Pharmaceuticals, Inc. considers it warranted not to conduct clinical trials in a population under 18 years of age.

FDA Response

Your rationale appears reasonable and it is likely that AA4500 will qualify for a waiver for pediatric development for the Dupuytren's indication. However, you will need to submit your rationale and the request for waiver with the BLA and the final determination will be made at that time.

Discussion: There was no further discussion on this question.

Question 16. Based on our current understanding of FDAAA and the product profile of AA4500 (i.e., NME), will the clinical program for AA4500 need to be reviewed by an Advisory Committee prior to approval?

FDA Response

The Division notes that AA4500 is a new molecular entity (NME) and that there is a higher likelihood that an Advisory Committee (AC) meeting will be convened for a NME. However, the determination of whether an AC meeting is necessary will be made once the BLA is submitted and the data are available for assessment.

Discussion: The Sponsor presented their rationale as to why an Advisory Committee meeting would not be warranted, and asked if the Division agreed with their assessment, and, if they could include data justifying this position in the BLA submission. The Division stated that the decision concerning an Advisory Committee meeting can not be made at this time; however, if desired, the Sponsor may submit materials to the BLA regarding their rationale for not needing an Advisory Committee meeting.

Additional Comments

1. **In the BLA, you should also provide subset analyses for the primary endpoint, including subgroups by:**
   a. **baseline demographics (age, gender, race, weight),**
   b. **baseline disease characteristics (e.g., stage of disease, degrees of contracture)**
   c. **investigational site.**

Discussion: The Sponsor asked the Division if it would be acceptable to perform subset analysis for primary endpoints using descriptive statistics. The Division stated that this was acceptable.

2. **Removal of the** (b) (4) **is not appropriate. You will need to continue to test the** (b) (4)

Discussion: The Sponsor requested that the Division provide a (b) (4) (b) (4)

3. **Provide a detailed description of the composition of the final drug product.**

Discussion: There was no further discussion on this comment.

4. **As part of the BLA, you will need to provide your procedures for preventing cross-contamination with other products manufactured at the multi-product facilities.**

Discussion: There was no further discussion on this comment.

5. **Follow ICH guideline M4Q(R1) "The common technical document for the registration of pharmaceuticals for human use: Quality – M4Q(R1). Quality overall summary of Module 2 Module 3: Quality." This document outlines what should be incorporated into Module 3 of the eCTD.**

Discussion: There was no further discussion on this comment.

6. **Verify whether or not you have received approval for a drug product name from USAN.**

Discussion: There was no further discussion on this comment.

7. **You will need to provide characterization data on the primary structure of AA4500 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., stability-indicating).**

Discussion: There was no further discussion on this comment.

8. **You will need to provide release and 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, you should perform all of your standard release assays as well as additional characterization tests. In addition, you should provide comparability data between the old and the new reference standards.**

Discussion: There was no further discussion on this comment.

In addition, we are also providing the following additional guidance regarding your planned BLA.

General Clinical Comments

The BLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the manual of policies and procedures (MAPP) 6010.3 at: http://www.fda.gov/cder/mapp/6010.3.pdf.

To facilitate the review, we request you provide analyses, where applicable, that will address the items in the template, including:

1. **Section 2.6 Other Relevant Background Information - important regulatory actions in other countries or important information contained in foreign labeling.**
2. **Section 5.3 Exposure-Response Relationships - important exposure-response assessments.**
3. **Section 7.1.6 - Less common adverse events (between 0.1% and 1%).**
4. **Section 7.1.7.3.1 - Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.**
5. **Section 7.1.7.3.2 - Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.**
6. **Section 7.1.7.3.3 - Marked outliers and dropouts for laboratory abnormalities.**

7. **Section 7.1.8.3.1 - Analysis of vital signs focused on measures of central tendencies.**
8. **Section 7.1.8.3.2 -Analysis of vital signs focused on outliers or shifts from normal to abnormal.**
9. **Section 7.1.8.3.3 -Marked outliers for vital signs and dropouts for vital sign abnormalities.**
10. **Section 7.1.9.1 – Overview of ECG testing in the development program, including a brief review of the nonclinical results.**
11. **Section 7.1.9.3. – Standard analyses and explorations of ECG data.**
12. **Section 7.1.16 – Overdose experience.**
13. **Section 7.4.2.1 - Explorations for dose dependency for adverse findings.**
14. **Section 7.4.2.2 - Explorations for time dependency for adverse findings.**
15. **Section 7.4.2.3 - Explorations for drug-demographic interactions.**
16. **Section 7.4.2.4 - Explorations for drug-disease interactions.**
17. **Section 7.4.2.5 - Explorations for drug-drug interactions.**
18. **Section 8.2 - Dosing considerations for important drug-drug interactions.**
19. **Section 8.3 - Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.**

Sites for Inspection

To assist the clinical reviewer in selecting sites for inspection, include a table in the original BLA for each of the completed Phase 3 clinical trials that has the following columns:

1. **Site number**
2. **Principle investigator**
3. **Location: City State, Country**
4. **Number of subjects screened**
5. **Number of subjects randomized**
6. **Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites**

7. **Number of protocol violations (Major, minor, definition)**

Common PLR Labeling Deficiencies

Highlights:

1. **Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI [See 21 CFR 201.57(d)(6) and Implementation Guidance].**

2. **The Highlights must be limited in length to one-half page, in 8 point type, two-column format [See 21 CFR 201.57(d)(8)].**

3. **The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product] [See 21 CFR 201.57(a)(1)].**
4. **For biologic products, the dosage form and route of administration must be on the next line (underneath the proper name) in the Highlights section [See 21 CFR 600.3 (k) and Section 351 of the PHS Act].**

5. **The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to**

   http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).

6. **For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge [See 21 CFR 201.57(d)(9) and Implementation Guidance].**

7. **The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:**

   "(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."

8. **Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.**

9. **Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).**

10. **A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)]**

11. **Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights. [See comment 34 Preamble]**

12. **The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION [See 21 CFR 201.57(a)(14)].**

13. **A revision date (i.e., Revised: month/year) must appear at the end of Highlights [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.**

14. **A horizontal line must separate the Highlights, Contents, and FPI [See 21 CFR 201.57(d)(2)].**

<u>Contents (Table of Contents):</u>

15. **The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI [See 21 CFR 201.57(b)].**

16. **The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded [See 21 CFR 201.57(d)(10)].**

17. **Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.**

18. **Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.**

19. **When a subsection is omitted, the numbering does not change.**

20. **[See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:**

    8.1 Pregnancy
    8.3 Nursing Mothers (not 8.2)
    8.4 Pediatric Use (not 8.3)
    8.5 Geriatric Use (not 8.4)

21. **When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading "Full Prescribing Information: Contents" must be followed by an asterisk and the following statement must appear at the end of the Contents:**

    "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI):

22. **Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).**

23. **Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format.**

24. **Do not refer to adverse reactions as "adverse events." Refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format," available at hhtp://www.fda.gov/cder/guidance.**

25. **The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, *[see Use in Specific Populations (8.4)]* not See *Pediatric Use (8.4).* The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance]**

26. **Include only references that are important to the prescriber [See 21 CFR 201.57(c)(16)].**

27. **Patient Counseling Information must follow after How Supplied/Storage and Handling section [See 21 CFR 201.56(d)(1)]. This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively [See 21 CFR 201.57 (c)(18)].**

28. **The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide [See 21 CFR 201.57(c)(18)]. The reference [See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.**

29. **There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.**
30. **The manufacturer information [See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics] should be located after the Patient Counseling Information section, at the end of the labeling.**

31. **Company website addresses are not permitted in labeling (except for a web address that is solely dedicated to reporting adverse reactions). Delete company website addresses from package insert labeling. The same applies to PPI and MG.**

32. **If the "Rx only" statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.**

33. **Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format.**

34. **Refer to the Institute of Safe Medication Practices' website (http://www.ismp.org/Tools/abbreviationslist.pdf) for a list of error-prone abbreviations, symbols, and dose designations.**

CDISC Data Requests to Sponsors
Quantitative Safety and Pharmacoepidemiology Group

Safety Analysis Plan

In conjunction with the Statistical Analysis Plan which generally addresses statistical issues for efficacy, include a Quantitative Safety Analysis Plan (QSAP). The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. The Clinical Data Interchange Standards Consortium (CDISC) Submission Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) outline the principles for data submission and analysis (www.cdisc.org).
At a minimum the Safety Analysis Plan should address the following components:

a. **Study design considerations (See: *FDA Guidance to Industry: Pre-Marketing Risk Assessment, http://www.fda.gov/CDER/guidance/6357fnl.pdf*).**

b. **Safety endpoints for Adverse Events of Special Interest (AERI)**

c. **Definition of Treatment Emergent Adverse Event (TEAE)**

d. **Expert adjudication process (Expert Clinical Committee Charter)**

e. **Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)**

f. **Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.**

g. **When unanticipated safety issues are identified the QSAP may be amended.**

Study Data Tabulation Model (SDTM) Issues

1. **The current published SDTM and SDTM Implementation Guide (SDTMIG) carefully should be followed. Refer to the SDTMIG section on Conformance (3.2.3)**

2. **Domains**
   a. **There are additional domains listed below that are not included in the current DTMIG. Information on these domains may be obtained at www.CDISC.org and are expected to be published in the next versions of SDTM and SDTMIG (Version 3.1.2). If applicable, use these domains.**
      - **(DV) Protocol deviations**
      - **(DA) Drug Accountability**
      - **(PC, PP) Pharmacokinetics**
      - **(MB, MS) Microbiology**
      - **(CF) Clinical Findings**

b. **The following domains are not available with SDTM but may be included if modeled following the principles of existing SDTM domains.**

- **Tumor information**
- **Imaging Data**
- **Complex Inclusion/Exclusion Criteria**

3. **Variables**

a. **All required variables are to be included.**

b. **All expected variables must be included in all SDTM datasets.**

c. **Variables (expected or permissible) for which no values will be submitted must be explicitly stated and discussed with the review division.**

d. **A list of all Permissible variables that will be included and those that will not be included for each domain must be provided for review and discussed with the review division.**

e. **A list and description of all variables that will be included in the Supplemental Qualifier dataset must be provided.**

f. **Do not include any variables in the SDTM datasets that are not specified in the SDTMIG.**

4. **Specific issues of note:**

a. **SDTM formatted datasets must not provide replication of core variables (such as treatment arm) across all datasets.**

b. **Only MedDRA preferred term and system organ class variables are allowed in the AE domain. However, the other levels of the MedDRA hierarchy may be placed in the SUPPQUAL dataset or an ADaM dataset.**

c. **These issues can be addressed through the request for ADaM datasets**

<u>Analysis Data Model (ADaM) Issues</u>

1. **Specify which ADaM datasets you intend to submit.**

2. **Include a list of all variables (including sponsor defined or derived) that will be included in the ADaM datasets.**

3. **Discuss the structure of the datasets with the reviewing division and specify in the QSAP.**

4. **Within each adverse event analysis dataset, include all levels of the MedDRA hierarchy as well as verbatim term.**

5. **Indicate which core variables will be replicated across the different datasets, if any.**

6. **SDTM and ADaM datasets must use the unique subject ID (USUBJID). Each unique subject identifier must be retained across the entire submission.**

General Items

Controlled terminology issues

a. **Use a single version of MedDRA for a submission. Does not have to be most recent version**

b. **We recommend that the WHO drug dictionary be used for concomitant medications.**

c. **Refer to the CDISC terminology for lab test names.**

d. **Issues regarding ranges for laboratory measurements must be addressed.**

Integrated Summary of Effectiveness

Please refer to the Guidance for Industry located at the following web page http://www.fda.gov/cder/guidance/7694dft.pdf

Dataset Comments

The Division requests the following for the submitted datasets:

1. **Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the division which studies are most appropriate for integration.**

The integrated safety dataset that must include the following fields/variables:

a. **A unique patient identifier**

b. **Study/protocol number**

c. **Patient's treatment assignment**

d. **Demographic characteristics, including gender, chronological age (not date of birth), and race**

e. **Dosing at time of adverse event**

f. **Dosing prior to event (if different)**

g. **Duration of event (or start and stop dates)**

h. **Days on study drug at time of event**

i. **Outcome of event (e.g. ongoing, resolved, led to discontinuation)**

j. **Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).**

k. **Marker for serious adverse events**

l. **Verbatim term**

2. **The adverse event dataset must include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset must also include the Verbatim term taken from the case report form.**

3. **See the attached mock adverse event data set that provides an example of how the MedDRA variables should appear in the data set. Note that this example only pertains to how the MedDRA variables must appear and does not address other content that is usually contained in the adverse event data set.**

4. **In the adverse event data set, provide a variable that gives the numeric MedDRA code for each lower level term.**

5. **The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire BLA. If this is not an option, then, at a minimum, it is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be very helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.**

6. **Provide a detailed description for how verbatim terms were coded to lower level terms according to the ICH MedDRA Term Selection: Points to Consider document.**

For example, were symptoms coded to syndromes or were individual symptoms coded separately.

7. **Perform the following SMQ's on the ISS adverse event data and include the results in your ISS report: 1. Severe cutaneous adverse reactions SMQ and 2. Possible drug related hepatic disorders – comprehensive search SMQ. Also, provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.**

8. **The spelling and capitalization of MedDRA terms must match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.**

9. **Also, for the concomitant medication dataset, you must use the standard nomenclature and spellings from the WHO Drug dictionary and include the numeric code in addition to the ATC code/decode.**

10. **For the laboratory data, be sure to provide normal ranges, reference ranges, and units as well as a variable that indicates whether the lab result was from the local lab or central lab. Also, the variable for the laboratory result must be in numeric format.**

11. **Perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.**

12. **In every dataset, all dates must be formatted as ISO date format.**

13. **Across all datasets, the same coding must be used for common variables, e.g. "PBO" for the placebo group. Datasets must not incorporate different designations for the same variable, e.g. "PBO" in one dataset, and "0 mg" or "Placebo," in another datasets. If the coding cannot be reconciled, another column using a common terminology for that variable must be included in the datasets.**

14. **All datasets must contain the following variables/fields (in the same format and coding):**
    a. **Each subject must have one unique ID across the entire BLA**
    b. **Study number**
    c. **Treatment assignment**
    d. **Demographic characteristics (age, race, gender, etc.)**

15. **A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities must be provided. Also, a listing must be provided of patients reporting adverse events involving abnormalities of laboratory values or**

vital signs, either in the "investigations" SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. The BLA analyses of the frequency of abnormalities across treatment groups are not sufficient without ready identification of the specific patients with such abnormalities. Analyses of laboratory values must include assessments of changes from baseline to worst value, not simply the last value.

16. **Provide CRFs for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events.**

17. **For patients listed as discontinued to due "investigator decision," "sponsor request," "withdrew consent," or "other," the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated.**

18. **With reference to the table on the following page, note that the HLGT and HLT level terms are from the primary MedDRA mapping only. There is no need to provide HLT or HLGT terms for any secondary mappings. This mock table is intended to address content regarding MedDRA, and not necessarily other data.**

Unique Subject Identifier (USUBJID)	Sequence Number (AESEQ)	Study Site Identifier (SITEID)	Unique Subject Identifier	Coding Dictionary Information	Reported Term for AE (Verbatim)	Lower Level Term MedDRA Code	Lower Level Term (LLT)	Preferred Term High Level Term (HLT)	High Level Group Term (HLGT)	System Organ Class (SOC)	Secondary System Organ Class 2 (SOC2)	Secondary System Organ Class 3 (SOC3)	Secondary System Organ Class 4 (SOC4)
01-701-1015	1	701	1015	MedDRA version 8.0	Redness around application site	10003058	Application site redness	Application site redness	Administration site reactions	General disorders and administration site conditions	Skin and subcutaneous tissue disorders		

Discussion: There was no further discussion on the additional guidance comments.

Major Points and Action Items for IND 5780

1. The Sponsor will provide data to clarify SEC- and RP-HPLC analysis and the use of the (b) (4) reference standards.

2. The Sponsor will provide a detailed justification as to why the spectrum generated during mass spectroscopy should not be used for comparability determination and the tables containing lot numbers and the studies that were used to highlight comparability. Data and rationale for these analytical comparability approaches must be submitted prior to submission of the BLA.

3. The Sponsor will provide justification for not performing additional nonclinical bridging studies. The Division recommended submitting the final nonclinical bridging study reports prior to submission of the BLA.

4. The Sponsor will perform sub-visible particle testing on the drug product for both release and stability testing.

5. The Sponsor will conduct pH testing of diluent.

6. The Sponsor will use polyclonal anti-serum in Western blot analyses to validate the new ELISA assay.

Linked Applications	Sponsor Name	Drug Name
'ND 5780	AUXILIUM PHARMACEUTICALS	Collagenase (C. histolyticum, Advance Biofactures)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHARON M TURNER RINEHARDT
10/08/2008

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 5780

Auxilium Pharmaceuticals, Inc
40 Valley Stream Parkway
Malvern, PA 19355

Attention: Diane P. Myers
Vice President, Quality Assurance and Regulatory Affairs

Dear Ms. Myers:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AA4500 Clostridial Collagenase.

We also refer to the meeting held on April 4, 2006, between representatives of your firm and this agency to discuss the development plans for AA4500 Clostridial Collagenase for the treatment of Dupuytren's contracture. A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1232.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

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

Memorandum

From: Bradley J. Glasscock, Pharm.D.

Subject: End-of-Phase 2/Pre-Phase 3 Teleconference

Sponsor: Lawrence C. Hurst, M.D.

Product: IND 5780, "Collagenase (C. histolyticum, Advance Biofactures)"

Indication: Treatment of Dupuytren's disease

Date, Location, & Time of Meeting: August 22, 2001
WOC-1, Conference Room 300N
2:00 - 3:30 p.m. (EST)

SUNY Representatives: Lawrence Hurst, Marie Badalamente

Biospecifics Technologies Corporation Representatives: Thomas Wegman, Bo Yu, Nina Dixon

FDA Representatives: Marc Walton, Dina Stolman, Barbara Buch, Malcolm Moos, Rona LeBlanc, Anne Pilaro, Bradley Glasscock, Diane Centeno-DeShield, Debra Lewis, Jeffery Fritsch

Summary:

Following introductions, the Agency provided the following comments on product, pre-clinical, and clinical issues:

Product

? Products issues appear to be acceptable for this stage of product development.
? Please provide additional information regarding the potency assay and the specifications in place to qualify this assay. This issue does not need to be addressed prior to initiating the Phase 3 study, but the potency assay will need to be reproducible for a potential biologics license application (BLA).

? Stability claims must be based on real-time data. To qualify the stability program, please demonstrate that the product meets all release criteria at the end of the stability dating period.

? Please consider the addition of a peptide map as a release test. This process would confirm that the manufacture of the product is under good control and may be used to support comparability studies that would be required in the case of any potential manufacturing changes.

? Please provide additional information on the Working Cell Bank (WCB).

? Please explain the extraneous sequencing result described in the July 12, 2001 CMC amendment to IND 5780.

? Please include internal controls for the limit of detection on all future SDS-PAGE analyses in an effort to control for variability in the purity assessment resulting from deviations in the gel staining/destaining procedure. Retrospective studies are needed only in the context of comparing Phase 2 to Phase 3 material.

? Since the Phase 2 material was manufactured using the "old" process, please provide comparability data (i.e., potency) between material manufactured under the "old" and "new" process. The sponsor stated that no material manufactured under the "new" process has been introduced into clinical studies to date.

? Validation data on the lifetime of the columns used in the manufacturing process, qualification of the (b) (4), and characterization of end-of-production cells will be required in a potential BLA.

? Please provide additional information on the immunogenicity assay.

? Please provide information on how the expiration dating for the intermediates ABC-I and ABC-II was determined.

? Please include either a test for host DNA in the final drug product as a release specification, or validate the process for its removal.

? Having no further issues to discuss, Malcolm Moos disconnected at this point in the teleconference.

Preclinical

? Preclinical requirements for chronic toxicity, reproductive toxicity, and carcinogenicity studies are waived due to the nature of the product, and its intended use in this specific clinical setting.

? Having no further issues to discuss, Anne Pilaro disconnected at this point in the teleconference.

Clinical

? The data presented show a dose response for the endpoint of reduction of flexion contracture and improved range of motion (ROM) for the response to a single dose. The choice of the 10,000 unit dose appears appropriate for the proposed Phase 3 study.

? There are not adequate data presented on the duration of response to a single dose, or to evaluate whether the regimen for a single or multiple doses would be optimal or necessary. The sponsor contends that most patients have a good response to a single dose, but that whether a patient will require additional doses and if so, how many, is a matter that requires individualized follow-up and ongoing evaluation.

? The use of open label re-treatments in this study has been advised against previously by CBER as not suitable for Phase 3 studies and does not allow for determination of duration of response for this particular product or the efficacy of subsequent injections. Please assess in the definitive efficacy trials, the durability of response out to 9 to 12 months, and obtain data regarding any potential changes in disease (i.e., worsening of adjacent joints, diathesis effects, etc.) at sites other than the target joint.

' The Agency will require sufficient and comprehensive data to enable writing adequate labeling for use of the product. Data will need to accurately describe treatment courses recommended for individual patients in order to achieve efficacy while maintaining an acceptable safety profile. Therefore, the approach to treatment needs to be carefully described in the protocol. This includes a treatment regimen that may allow for evaluation and additional injections given so as to maintain the blinded, controlled design of the study. Please prospectively define the criteria for dose adjustment and modification, as well as the treatment regimen for patients that may require additional treatments.

? As stated previously in our letter of May 18, 1999, please be aware that a single Phase 3 study is not adequate to assess the efficacy of this product, and this study, alone, will be inadequate to support a potential marketing application. The Agency requests that at least two studies with sufficiently large patient populations be conducted in order to assess the safety and efficacy of the product. The Agency considers the proposed Phase 3 study conducted at two sites to be one study. Additional studies should support the proposed dose and regimen as well as provide a larger safety database to assess the rate of occurrence for specific adverse events.

? The current protocol includes numerous operator-dependent techniques that may limit the generalizability of the treatment. Please describe these techniques in sufficient detail that would allow for these techniques to be reproduced in future studies at other study centers, and adequately described in labeling.

? Please include explicit description with regard to injection techniques, post-injection joint manipulation, splint usage, and ROM exercises in the Phase 3 protocol. Please include any patient instruction information as well.

? The safety database for a potential BLA will need to be sufficiently large enough to provide a reasonable degree of confidence that allows for assessment of adverse events, antibody response, and immune response.

? Please define the patient population targeted for the proposed Phase 3 protocol with respect to inclusion/exclusion criteria to ensure that end-stage patients only are included in the study. Also, please include more detail regarding the inclusion of patients with diathesis.

? The proposed primary efficacy endpoint is a composite of reduction of contracture and improvement in range of motion. We agree this is appropriate. However, the amount of improvement required to demonstrate improved range of motion should be defined and the examination technique should be clearly stated. The proposed secondary endpoints are appropriate for this type of study, including survival analysis of the time to reduction in contracture, and the change from baseline in grip strength. The proportions of patients who subsequently require surgery should also be considered as a secondary endpoint.

' The primary analysis should be based on the intent to treat (ITT) population, defined as all patients randomized to treatment, regardless of whether the patient received the study drug. A secondary analysis may be performed for all evaluable patients.

? Clearly specify the randomization and stratification methods employed for the Phase 3 study.

? Due to the potential for unblinding due to the effects of treatment, please describe the measures in place to encourage compliance of placebo patients with regard to splint requirements and physical therapy exercises.

? The CRFs presented should be revised. Due to time limitations, comments on the CRF may be provided in future discussions.

? Please provide the Agency with a revised Phase 3 protocol incorporating the discussion points listed above. The Agency welcomes the opportunity to comment on this revised protocol in future discussions.

NDA/BLA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

Application Information		
NDA # BLA# 125338	NDA Supplement #:S- BLA STN # 0	Efficacy Supplement Type SE-
Proprietary Name: under review Established/Proper Name: clostridial collagenase Dosage Form: Injections Strengths:		
Applicant: Auxilium Pharmaceuticals, Inc. Agent for Applicant (if applicable): N/A		
Date of Application: 2/27/2009 Date of Receipt: 2/27/2009 Date clock started after UN:		
PDUFA Goal Date: 8/28/2009	Action Goal Date (if different):	
Filing Date: 4/28/2009 Date of Filing Meeting: 3/26/2009		
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed Indication(s): Non-surgical treatment of advanced Dupuytren's disease		
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 X 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 X 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): BB-IND 5780	
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.***	X 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.***	X 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.***	X 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 X NO ☐ YES ☐ NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	X YES NO
User Fee Status **Comments:**	Paid X 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 X 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)*** ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.* **Comments:** However, seven years of orphan exclusivity was requested.	☐ 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.***	**X** Not applicable ☐ YES NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
	X 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) X All electronic ☐ Mixed (paper/electronic) X 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**:	X 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):	X YES ☐ NO

Form 356h: Is a signed form 356h included? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.*** Are all establishments and their registration numbers listed on the form? **Comments:**	X YES ☐ NO X YES ☐ NO
Index: Does the submission contain an accurate comprehensive index? **Comments:**	X 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 X English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain:	X 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:**	X 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:**	X YES ☐ NO
Debarment Certification	
Correctly worded Debarment Certification with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.***	X YES ☐ NO

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:**	X 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? **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) **Comments:**	X Not Applicable YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO

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 X NO
Prescription Labeling	
Check all types of labeling submitted. **Comments:**	☐ **Not applicable** X Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use ☐ MedGuide Carton labels X Immediate container labels ☐ Diluent ☐ Other (specify)
Is electronic Content of Labeling submitted in SPL format? ***If no, request in 74-day letter.*** **Comments:**	X 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:**	X YES ☐ NO ☐ YES ☐ NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **Comments:**	X YES ☐ NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (*send WORD version if available*) **Comments:**	X Not Applicable YES ☐ NO
REMS consulted to OSE/DRISK? **Comments:**	X Not Applicable ☐ YES ☐ NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP? **Comments:**	☐ Not Applicable X 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**: Teleconference	X YES Date(s):August 22, 2001 NO
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments:**	X YES Date(s): September 15, 2008 NO
Any Special Protocol Assessment (SPA) agreements? ***If yes, distribute letter and/or relevant minutes before filing meeting.*** **Comments:**	YES Date(s): X NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 3-26-2009

~~NDA/~~BLA #: 125338

PROPRIETARY/ESTABLISHED NAMES: clostridial collagenase for Injection

APPLICANT: Auxilium Pharmaceuticals, Inc.

BACKGROUND: 505(b)(1) referenced on three clinical studies.
The related BB-IND is 5780:
August 22, 2001: End-of Phase 2 meeting/teleconference
September 15, 2008: Pre-NDA meeting (meeting minutes in DARRTS).

(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:	Margarita Tossa	Y
	CPMS/TL:	Sara Stradley	Y
Cross-Discipline Team Leader (CDTL)	Sarah Okada, M.D.		Y
Clinical	Reviewer:	Eric Brodsky, M.D.	Y
	TL:	Sarah Okada, M.D.	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
OSE	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Srikanth Nallani, PhD	Y
	TL:	Suresh Doddapaneni, PhD	N
Biostatistics	Reviewer:	Jonathan Norton, PhD	Y
	TL:	Dionne Price, PhD	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Asoke Mukherjee, PhD	Y
	TL:	Dan Mellon, PHD	Y
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Ashutosh Rao, PhD	Y
	TL:	Kathy Lee, PhD	Y
Facility (*for BLAs/BLA supplements*)	Reviewer:		
	TL:		
Microbiology, sterility (*for NDAs/NDA efficacy supplements*)	Reviewer:	Anastasia Lolas/Kalavati Suvarna	Y/Y
	TL:	Patricia Hughes	N
Bioresearch Monitoring (DSI)	Reviewer:	Roy Blay	
	TL:	Constance Lewin	
Other reviewers			

OTHER ATTENDEES: Bob Rappaport, Jeffrey Siegel, Rigoberto Roca, Mary Dempsey, Chris Wheeler, Thomas Prmutt

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

Electronic Submission comments **List comments:**	☐ Not Applicable
CLINICAL **Comments:**	☐ Not Applicable X FILE ☐ REFUSE TO FILE X Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: This NDA submission is based on published literature.	X 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***	X YES Date if known: X 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 X NO
CLINICAL MICROBIOLOGY **Comments:**	Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY	☐ Not Applicable X FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES NO
BIOSTATISTICS **Comments:**	Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments:**	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments:**	☐ Not Applicable X FILE ☐ REFUSE TO FILE X 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**: see CMC review in DFS ()	☐ Not Applicable X YES ☐ NO ☐ YES ☐ NO ☐ YES NO
• Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments:**	☐ Not Applicable X YES ☐ NO ☐ Not Applicable ☐ YES ☐ NO
• Sterile product? **If yes**, was Microbiology Team consulted for validation of sterilization? **(NDAs/NDA)**	☐ YES NO ☐ YES ☐ NO

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

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Curt Rosebraugh, MD

GRMP Timeline Milestones: Mid-Cycle- ; Wrap-Up- ; Action Package to DD- ; Action Goal Date- .8/28/2009

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. X Review issues have been identified for the 74-day letter. List (optional): Standard Review X 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