# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**125338**

# MICROBIOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 51
Silver Spring, MD 20993

**Date:** 27 October 2009
**To:** Administrative File, STN 125338/0
**From:** Patricia F. Hughes, Ph.D., CDER/OC/DMPQ/BMT PFH 10/27/09
**Subject:** New BLA
**Applicant:** Auxilium Pharmaceuticals, Inc.
**Mfg Facilities:** **Drug Substance:** Auxilium Pharmaceuticalss, Inc. Horsham, PA, FEI=3006537159
**Drug Product** (b) (4)

**Product:** Xiaflex™ (collagenase clostridium histolyticum)
**Dosage:** Sterile lyophilized powder in a 3 mL glass vial (0.9 mg) for intralesional injection following reconstitution with the provided diluent (5 mL glass vial, 3 mL fill)
**Indication:** Treatment of advanced Dupuytren's disease
**Due Date:** 13 November 2009

## Recommendation for Approvability

## CMC Microbiology:

The BLA 125338, as amended, is recommended for approval from product quality microbiology perspective. Two post-marketing requirements (PMRs) and three post-marketing commitments (PMCs) are recommended.

The PMRs are as follows:

1. 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 in a CBE supplement by March 2010.*

2. Determine the $D_{121}$-value of the biological indicator *G. stearothermophilus* in the diluent product solution and reassess the validation studies conducted. Provide a

comparison to the D-values used in the product validation studies. *Submit data in a CBE supplement by March 2010.*

The PMCs are as follows:

3. Conduct a study to demonstrate microbial control at end of hold (10 days) for the individual AUX-I and AUX-II intermediates. The hold time study included in the submission for the individual AUX-I and AUX-II intermediates is inadequate as the study was performed using formulation buffer. *Submit the data from the study in a CBE-30 supplement by December 2010.*

4. Qualify the bioburden test for in-process intermediates. The qualification should be performed using 3 different lots. *Submit the data in a CBE-30 supplement by December 2010.*

5. The endotoxin test was qualified using one lot of AUX-I and AUX-II intermediates, and one lot of drug substance. Please perform additional qualification using 2 lots of AUX-I intermediate, AUX-II intermediate, and drug substance, and 3 lots of HIC eluate and TFF-1 concentrate, to demonstrate reproducibility of the test results. *Submit the summary data in a CBE-30 supplement by December 2010.*

## CGMP Acceptability of Establishments:

The manufacturing and testing facilities listed in the BLA are currently in compliance with CGMP requirements and there are no pending compliance actions that would prevent approval of this BLA. The drug substance manufacturing facility, Auxilium, in Horsham, PA, was inspected by a team of investigators (Anastasia Lolas, Kathy Lee and Ashutosh Rao) August 17-21, 2009. A 3 item FDA form 483 was issued to the firm. However, all inspectional observations were adequately resolved and the facility was classified as acceptable from a CGMP perspective. The inspection of the drug product manufacturing facility, (b) (4), was waived based on the current acceptable cGMP status. (b) (4) is an analytical testing site used an alternate release and stability testing site. The site was inspected on October 5-6, 2009 and has an acceptable CGMP status.

## Summary

The drug product Xiaflex™ (collagenase clostridium histolyticum) is for the treatment of advanced Dupuytren's disease. The finished dosage form is a single dose, sterile, white lyophilized powder for intralesional injection following reconstitution with the provided diluent. It is supplied in 3 mL glass vial (0.9 mg) to deliver 0.58 mg injection volumes of 0.20 or 0.25 mL. The diluent consists of a solution of 0.03% calcium chloride dihydrate

(b) (4) in 0.9% sodium chloride (b) (4) with (b) (4) and is packaged in a 5 mL glass vial (3 mL) fill).

(b) (4)

(b) (4)

The following PMRs should be communicated to the sponsor:

1. 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 in a CBE supplement by March 2010.

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

(b) (4)

2. Determine the $D_{121}$-value of the biological indicator *G. stearothermophilus* in the diluent product solution and reassess the validation studies conducted. Provide a comparison to the $D_{121}$-values used in the product validation studies. *Submit data in a CBE supplement by March 2010.*

(b) (4)

The following PMCs should be communicated to the sponsor:

1. Conduct a study to demonstrate microbial control at end of hold (10 days) for the individual AUX-I and AUX-II intermediates. The hold time study included in the submission for the individual AUX-I and AUX-II intermediates is inadequate as the study was performed using formulation buffer. *Submit the data from the study in a CBE-30 supplement by December 2010.*

(b) (4)

(b) (4) The completion of these studies should be reported as a post marketing commitment.

2. Qualify the bioburden test for in-process intermediates. The qualification should be performed using 3 different lots. Submit the data in a CBE-30 supplement by December 2010.

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.

3. The endotoxin test was qualified using one lot of AUX-I and AUX-II intermediates, and one lot of drug substance. Please perform additional qualification using 2 lots of AUX-I intermediate, AUX-II intermediate, and drug substance, and 3 lots of HIC eluate and TFF-1 concentrate, to demonstrate reproducibility of the test results. *Submit the summary data in a CBE-30 supplement by December 2010.*

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.

## Conclusions:

I. The BLA, as amended, is recommended for approval from a microbiology product quality perspective.

II. Information and data in the CMC sections of the BLA not related to microbiology product quality were assessed by OBP/DTP reviewers.

III. The manufacturing and testing facilities listed in the BLA are currently in compliance with CGMP requirements and there are no pending compliance actions that would prevent approval of this BLA. The pre-approval inspection of the contract manufacturer, (b) (4) was waived based on the current acceptable GMP status of the facility.

Cc: WO Bldg 51, Hughes
WO Bldg 51, Lolas
WO Bldg 51, Suvarna
WO, Bldg 51 Thomas
WO, Bldg 22, Tossa
WO Bldg 51, e-CTD files (STN 125338)

Archived File: S:\archive\BLAs\1253338\125338.0.TL.rev.mem.BLA.10-26-2009.doc

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

**Date:** 21 October 2009

**To:** Administrative File, STN 125338

**From:** Anastasia G. Lolas, Microbiologist, OC/DMPQ/MAPCB/BMT AL 10/22/09
Colleen Thomas Ph.D., Microbiologist, OC/DMPQ/MAPCB/BMT CT 22 OCT 09

**Through:** Patricia Hughes, Ph.D., Team Leader, OC/DMPQ/MAPCB/BMT

**Subject:** New Biologics License Application

**Applicant:** Auxilium Pharmaceuticals, Inc.

**Facility:** DS – Auxilium Pharmaceuticals, Inc., Horsham, PA (FEI 3006537159)
DP – (b) (4)

**Product:** Xiaflex™ (collagenase clostridium histolyticum)

**Dosage:** Sterile lyophilized powder in a 3 mL glass vial (0.9 mg) for intralesional injection following reconstitution with the provided diluent (5 mL glass vial, 3 mL fill)

**Indication:** Treatment of advanced Dupuytren's disease

**Due date:** 28 August 2009

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**Recommendation for Approvability:** STN 125338/0 is recommended for approval from a microbial control, sterility assurance and microbiology product quality perspective with two post-marketing requirements:

1. 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 v*alidation report and data in a CBE supplement by March 2010.*

2. Determine the $D_{121}$-value of the biological indicator *G. stearothermophilus* in the diluent product solution and reassess the validation studies conducted. Provide a comparison to the D-values used in the product validation studies. *Submit data in a CBE supplement by March 2010.*

The Auxilium Pharmaceuticals, Inc. drug substance manufacturing site in Horsham, PA was inspected on August 17-21, 2009. The inspection was classified VAI with three FDA 483 observations. NGDMT/DMPQ has reviewed the firm's responses and found them acceptable. The (b) (4). analytical testing site was inspected October 5-6, 2009. There were no

observations and the inspection was classified as No Action Indicated (NAI). A memo is included in the final action package waiving the inspection of the drug product (b) (4) manufacturing site.

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## Review Summary

Auxilium Pharmaceuticals, Inc. submitted STN 125338/0 on 27-Feb-2009 to license Xiaflex™ (collagenase clostridium histolyticum) and the associated manufacturing processes. The application has an orphan drug designation and is a priority review with a PDUFA user fee date of 28-Aug-2009. The OND clinical division (DAARP) has assigned a tentative action date of 15-Oct-2009 as the advisory committee meeting was scheduled for 16-Sep-2009.

The BLA is an electronic submission in CTD format. The referenced IND is BB-IND 5780.
The drug substance facility in Horsham, PA was not registered at the time of the filing meeting on 26-Mar-2009. Following communications with the applicant and further internal communications, the facility was registered on 02-Apr-2009 and a production schedule was submitted as an amendment on 09-Apr-2009. A total of 4 lots were to be manufactured starting 05-May-2009. The inspection was scheduled initially for June 1-5, 2009 during the manufacture and purification activities of Lot D. However, the inspection was postponed to a later date (b) (4) . There were several teleconferences with Auxilium, conducted with the help of the OND Division. The inspection was conducted on August 17-21, 2009 after resolution of the contamination issue. It was classified VAI with three FDA 483 observations. The firm's responses have been reviewed by NGDMT/DMPQ and found adequate.

The following amendments related to CMC-microbiology were reviewed:

- 27-Mar-2009 (sequence 0002) – addition of contract packaging and labeling site (b) (4)
- 09-Apr-2009 (sequence 0003) – production schedule for DS
- 14-Apr-2009 (sequence 0005) – response to CMC-microbiology questions
- 16-Jun-2009 (sequence 0007) – labeling
- 02-Jul-2009 (sequence 0010) – shipping validation
- 09-Jul-2009 (sequence 0012) – stability update
- 21-Aug-2009 (sequence 0019) – response to CMC-microbiology IR of 27-Jul-2009
- 25-Aug-2009 (sequence 0021) – response to CMC-microbiology IR of 14 and 17-Aug-2009
- 25-Aug-2009 (sequence 0022) – labeling
- 27-Aug-2009 (sequence 0023) – labeling
- 24-Sep-2009 (sequence 0034) – response to CMC-microbiology IR of 14-Sep-2009
- 25-Sep-2009 (sequence 0035) – response to CMC-microbiology IR of 18-Sep-2009

This review addresses only the lyophilized drug product and the companion diluent manufacturing processes. A separate review has been written for the drug substance manufacturing process. Colleen Thomas reviewed the container-closure integrity, sterility testing, endotoxin testing and the lyophilization cycle validation.

(b) (4)

33 Pages Withheld as b(4) Trade Secret/Confidential

**From:** Stock, Marisa
**Sent:** Wednesday, October 21, 2009 12:42 PM
**To:** Lolas, Anastasia
**Cc:** CDER-TB-EER
**Subject:** RE: BLA 125338

**Attachments:** BLA 125338 Site Compliance Status.doc

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER for BLA 125338. Please see the attachment below to find the compliance status of each facility. There are no pending or ongoing compliance actions to prevent approval of BLA 125338 at this time.

BLA 125338 Site Compliance Sta...

**Marisa Stock**
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DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
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**Date:** August 31, 2009
**To:** Administrative File, STN 125338/0
**From:** Kalavati Suvarna, Ph.D., CDER/OC/DMPQ/MAPCB/BMT 10/20/09
**Endorsement:** Patricia Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/MAPCB/BMT 10/22/09
**Subject:** Original BLA
**US License:** 1816
**Applicant:** Auxilium Pharmaceuticals, Inc.
**Mfg Facility:** **For drug substance:** Auxilium Pharmaceutical, Inc.
102 Witmer Road, Horsham, PA 19044. USA
FEI No. 3006537159
**Product:** Xiaflex™ (D, M histolase, AA4500, Clostridial collagenase)
**Dosage:** Lyophilized powder for injection (0.58 mg)
**Indication:** Treatment of advanced DuPuytren's disease
**Due Date:** October 23, 2009

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**Recommendation for Approvability:** The BLA, as amended, is recommended for approval from a microbiology product quality perspective with the following post-marketing commitments:

Post-marketing commitment 1: Please conduct a study to demonstrate microbial control at end of hold (10 days) for the individual AUX-I and AUX-II intermediates. The hold time study included in the submission for the individual AUX-I and AUX-II intermediates is inadequate as the study was performed using formulation buffer. The data from the study should be submitted in a CBE-0 supplement by December 2010.

Post-marketing commitment 2: Please qualify the bioburden test for in-process intermediates. The qualification should be performed using 3 different lots. The data should be submitted in a CBE-0 supplement by December 2010.

Post-marketing commitment 3: The endotoxin test was qualified using one lot of AUX-I and AUX-II intermediates, and one lot of drug substance. Please perform additional qualification using 2 lots of AUX-I intermediate, AUX-II intermediate, and drug substance, and 3 lots of HIC eluate and TFF-1 concentrate, to demonstrate reproducibility of the test results. The data should be submitted in a CBE-0 supplement by December 2010.

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## SUMMARY:

AA4500 is a parenteral lyophilized powder consisting of (b) (4) ratio of two purified collagenases, AUX-I (Clostridial type I collagenase) and AUX-II (Clostridial type II collagenase) from *Clostridium histolyticum* (non-recombinant) for the treatment of advanced DuPuytren's disease and is the subject of BLA 125338. The BLA was submitted in eCTD format. This review covers the evaluation of the drug substance aspects of the application from a microbial control and microbiology product quality perspective. The commercial manufacturing site for AA4500 drug substance is Auxilium Pharmaceutical, Inc located in Horsham, PA. The original submission and amendments to the original submission (eCTD sequence numbers: 0002 dated 3/27/2009; 0003 dated 4/9/2009; 0005 dated 4/14/2009; 0010 dated 7/2/2009; 0012 dated 7/9/2009; 0019 dated 8/21/2009; and 0020 dated 8/19/2009) are reviewed here.

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## ASSESSMENT:

This is a new BLA requesting approval of AA4500, a purified Clostridial Collagenase for the treatment of advanced DuPuytren's disease. It is a parenteral lyophilized powder consisting of (b) (4) ratio of two collagenases, AUX-I (Clostridial type I collagenase) and AUX-II (Clostridial type II collagenase). These collagenases are excreted by the bacterium *Clostridium histolyticum.* The manufacturing process consists of (b) (4) (b) (4)

The application contains information to support commercial production of AA4500 drug substance at Auxilium Pharmaceutical, Inc located in Horsham, PA, as well as drug product manufacture a (b) (4)a.

This assessment only covers the drug substance aspects of the application. For drug product aspects of the application, please see the review by Ms. Anastasia Lolas and Dr. Colleen Thomas.

### 3.2.S. DRUG SUBSTANCE

### 3.2.S.1. GENERAL INFORMATION

AA4500 drug substance consists of two collagenases referred to as AUX-I and AUX-II manufactured by (b) (4) the bacterium *Clostridium histolyticum.* (b) (4) (b) (4)

This section should be reviewed by OBP/DTP reviewer.

25 Pages Withheld as b(4) Trade Secret/Confidential