CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201811Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 24 February 2015

TO: NDA 201-811

FROM: Denise Miller
CDER/OPQ/OPF/DMA/Branch II, Microbiologist

THROUGH: Neal J. Sweeney Ph.D.
CDER/OPQ/OPF/DMA/Branch II, Senior Microbiologist

SUBJECT: NDA 201811
Product: Argatroban Injection
Sponsor: Fresenius Kabi

The subject submission is a resubmission of the NDA 201-811 dated 23 January 2015 providing responses to a 28 February 2014Complete Response letter. The CR letter identifies facility inspection deficiencies.

A quality microbiology review was completed on 29 June 2012 recommending approval of the NDA. The subject resubmission contains no new product quality microbiology information for review.

Reviewer's Comment: NDA 201-811 is recommended for approval from a quality microbiology perspective.

Reviewer's Signature Denise Miller -A
Digitally signed by Denise Miller -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Denise Miller -A, 0.9.2342.19200300.100.1.1=2000286872
Date: 2015.02.25 15:41:44 -05'00'

Denise A. Miller
Microbiologist, OPF/DMA/Branch II

Endorsement Block Neal J. Sweeney -A
Digitally signed by Neal J Sweeney A
DN: c=US o=U S Government ou=HHS ou=FDA ou=People
0 9 2342 19200300 100 1 1=1300109587 cn=Neal J Sweeney A
Date: 2015 02 25 15:45:04 05'00'

Neal J. Sweeney, Ph.D.
Senior Microbiologist, OPF/DMA/Branch II

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 31 January 2014

TO: File: NDA 201811

FROM: John W. Metcalfe, Ph.D.
Senior Review Microbiologist
CDER/OPS/New Drug Microbiology Staff
(301) 796-1576

THROUGH: Stephen Langille, Ph.D.
Senior Review Microbiologist
CDER/OPS/New Drug Microbiology Staff

SUBJECT: NDA 201811
Submission Date: 13 September 2013 (NDA Resubmission)
Drug Product: Argatroban Injection
Sponsor: Fresenius Kabi (formerly APP)

The subject submission is a resubmission of the NDA providing responses to a Complete Response letter (dated 05 April 2013). The CR letter identifies both chemistry and facility inspection deficiencies.

A review was completed on 29 June 2012 recommending approval of the NDA from the standpoint of product quality microbiology. The subject resubmission contains no new product quality microbiology information for review.

Reviewer's Comment
NDA 201811 is recommended for approval from the standpoint of product quality microbiology.

END

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/s/

JOHN W METCALFE
01/31/2014

STEPHEN E LANGILLE
01/31/2014

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 25 February 2013

TO: File: NDA 201811

FROM: John W. Metcalfe, Ph.D.
Senior Review Microbiologist
CDER/OPS/New Drug Microbiology Staff
(301) 796-1576

THROUGH: Bryan S. Riley, Ph.D.
Senior Review Microbiologist
Acting Team Leader
CDER/OPS/New Drug Microbiology Staff

SUBJECT: NDA 201811
Submission Date: 12 October 2012 (NDA Resubmission)
Drug Product: Argatroban Injection
Sponsor: Fresenius Kabi (formerly APP)

The subject submission is a resubmission of the NDA providing responses to a Complete Response letter (dated 23 July 2012). The CR letter identifies both chemistry and facility inspection deficiencies.

A review was completed on 29 June 2012 recommending approval of the NDA from the standpoint of product quality microbiology. The subject resubmission contains no new product quality microbiology information for review.

Reviewer's Comment
NDA 201811 is recommended for approval from the standpoint of product quality microbiology.

END

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/s/

JOHN W METCALFE
02/25/2013

BRYAN S RILEY
02/25/2013
I concur.

Product Quality Microbiology Review

29 June 2012

NDA: 201811/N-000

Drug Product Name
Proprietary: N/A
Non-proprietary: Argatroban Injection.

Review Number: 2.

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
31 JAN 2012	31 JAN 2012	31 JAN 2012	03 FEB 2012
07 JUN 2012	08 JUN 2012	N/A	N/A

Submission History (for amendments only)

Submit Date(s)	Microbiology Review #	Review Date(s)
02 APR 2010	1	13 JAN 2011

Applicant/Sponsor
Name: APP Pharmaceuticals, LLC.
Address: 1501 East Woodfield Rd.
Suite 300E
Schaumburg, IL 60173
Representative: Aditi Dron
Telephone: 847-330-3898

Name of Reviewer: John W. Metcalfe, Ph.D.

Conclusion: Recommend approval.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: NDA Resubmission.

2. SUBMISSION PROVIDES FOR: Response to Complete Response letter.

3. MANUFACTURING SITE:
APP Pharmaceuticals, LLC
3159 Staley Road
Grand Island, NY 14072

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:
- Solution in (b) (4) glass vial.
- Intravenous Injection.
- 100 mg/mL.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Anticoagulant.

B. SUPPORTING/RELATED DOCUMENTS:
- Microbiology Review of DMF (b) (4); dated 07 June 2011.
- Microbiology Review #1 of NDA 201811; dated 13 January 2011.
- Microbiology Review of ANDA 91516; dated 23 March 2012.

C. REMARKS:
Microbiology Review #1 concluded the NDA to be "approvable" on the basis that during the review cycle, the proposed drug product manufacturing facility (APP/Barceloneta) was closed (summer of 2010). The subject submission identifies a different APP site for the manufacture of the drug product.

A microbiology information request was provided to the OND project manager on 18 April 2012 by this reviewer to be forwarded to the applicant. Following is the information request:

A microbiology review of NDA 201811 is in progress. Please provide the following information or reference to its location in the subject submission:

- *Clarification with regard to when in the drug product manufacturing process the sample is taken for bioburden determination. Figure 3.2.P.3.3-1 depicts that the sample is taken* (b) (4) *. However, Section 1.1 of Module 3.2.P.3.5 provides a limit of NMT* (b) (4) *CFU/mL for the "* (b) (4) *test method validation". Clarify this discrepancy.*

- *Clarification with regard to the performance of media fill process simulations. Section 4.5 of Module 3.2.P.3.5 states that a* [redacted] (b) (4) *units are filled. Further, it is stated in Section 5 (Actions concerning Production when media fills fail) that a* [redacted] (b) (4) *vials must be filled and incubated. However, the media fill data reported in the application (batches 7020719, 7020718 and 7020795) demonstrate that (only)* [redacted] (b) (4) *vials were filled. Clarify this discrepancy.*
- *A rationale regarding how the media fill data reported in the application (batches 7020719, 7020718 and 7020795) support the subject drug product manufacturing process. Each of the* [redacted] (b) (4) *process simulations utilized* [redacted] (b) (4) *mL vials with either a* [redacted] (b) (4) *mL or* [redacted] (b) (4) *mL fill volume, while the subject drug product is comprised of a* [redacted] (b) (4) *vial with a 2.5 mL fill volume.*
- *The SOP 03-10-08-0017 (Finished Product/Raw Material BET Validation Procedure Using Kinetic Turbidimetric Analysis) and the test method used for bacterial endotoxins testing of the finished drug product. The narrative provided in the Microbiological Method Validation Package describes a study that was performed to verify the suitability of use of the bacterial endotoxins test with the subject drug product. The narrative states that the slope of the standard curve, the positive control, the standard curve correlation coefficient, and the negative control all met specification, however the acceptance criteria for each of these are not provided.*

The applicant provided a response to this information request on 08 June 2012. The responses are summarized and reviewed in appropriate sections of this review.

File Name: N201811R2.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – NDA 201811/N-000 is recommended for approval on the basis of issues pertaining to product quality microbiology.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – Not applicable.

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology - (b) (4)

B. Brief Description of Microbiology Deficiencies – There are no microbiology deficiencies identified.

C. Assessment of Risk Due to Microbiology Deficiencies – Not applicable.

III. Administrative

A. Reviewer's Signature _____

John W. Metcalfe, Ph.D.
Senior Microbiology Reviewer
CDER/OPS/NDMS

B. Endorsement Block_____

Stephen E. Langille, Ph.D.
Senior Microbiology Reviewer
CDER/OPS/NDMS

C. CC Block

N/A

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

S DRUG SUBSTANCE

The drug substance manufacturing process is not the subject of this review since the subject drug product is sterilized during the drug product manufacturing process.

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Description of drug product**
  The subject drug product is a sterile solution which is presented in a (b) (4) amber glass vial.

- **Drug product composition**
  The drug product composition is presented in Table 1 which is copied from Module 3.2.P.1.1.

Table 1. Drug Product Composition.

Argatroban Injection	Unit Dose	Exhibit Batches			Proposed Commercial Batch
		S780004	S780013	S780014	
Strength	100 mg/mL				
Packaging Configuration	2.5 mL fill in a (b) (4) vial				
Product Code	Code 512603				
Batch Size (b) (4)	N/A	(b) (4)			
Batch Size (vials)	N/A				
Ingredient	Ingredient Amount/mL				
Argatroban	100 mg				
Propylene Glycol, USP	Q.S.				

(b) (4)

(b) (4)

- **Description of container closure system**
  Following are the container closure components (source-Table 3.2.P.7-2):
  - Container: Amber, Type 1 USP glass. (b) (4) via (b) (4) (b) (4)
  - Closure: 13 mm, (b) (4)
  - Seal: 13 mm, aluminum, flip cap seal (b) (4)

Reviewer's Comment

The applicant's specifications for the vial critical dimension values are provided in Module 3.2.P.7. The specifications for the vial inner and outer diameters are (b) (4) inches, respectively. The applicant states that both the (b) (4) Type 1

glass vials comply with these specifications. The allowable inner diameter specification varies by less than [redacted] (b) (4). This is very small and consequently, container closure integrity testing using one of the containers to be included in the drug product should be representative of both the [redacted] (b) (4) containers.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- **Container-Closure and Package integrity**

The application contains a narrative describing the [redacted] (b) (4). This system was used to assess the integrity of the container closure system and works by [redacted] (b) (4) (Module 3.2.P.2.2).

The subject submission contains data from the testing of three batches of product (R340-032, 340-033 and 340-034) using the [redacted] (b) (4). The following is copied from the method summary of SOP #10-08-00-6031 and summarizes how the test is performed:

[redacted] (b) (4)

Each of the batches run met stated acceptance criteria for this container closure integrity test.

Satisfactory

Reviewer's Comment

The subject leak testing system was described in ANDA 91516 which is also held by APP Pharmaceuticals, LLC. Microbiology Review of ANDA 91516 (dated 23 March 2012) concluded the [redacted] (b) (4) to be an acceptable container closure integrity testing system and provided several references to published studies linking the size of a container breach capable of inhibiting microbial ingress with the failure limit of the stated test (the DP value obtained from a [redacted] (b) (4)).

- **Preservative Effectiveness**
  The subject drug product is not preserved.

P.3 Manufacture

P.3.1 Manufacturer

APP Pharmaceuticals, LLC
3159 Staley Road
Grand Island, NY 14072

P.3.3 Description of the Manufacturing Process and Process Controls

(b) (4)

Satisfactory

(b) (4)

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(b) (4)

This reviewer attended the labeling meetings and conveyed the labeling modifications identified above to the review team who implemented the reviewer's suggestions.

2. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

There are no microbiology deficiencies identified.

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/s/

JOHN W METCALFE
06/29/2012

STEPHEN E LANGILLE
06/29/2012

Product Quality Microbiology Review

13 January 2011

NDA: 201,811

Drug Product Name
Proprietary: N/A.
Non-proprietary: Argatroban Injection.

Review Number: 1.

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
02 APR 2010	05 APR 2010	14 APR 2010	15 APR 2010
01 JUL 2010	02 JUL 2010	N/A	N/A

Applicant/Sponsor
Name: APP Pharmaceuticals, LLC.
Address: 1501 East Woodfield Rd.
Suite 300E
Schaumburg, IL 60173
Representative: Aditi Dron
Telephone: 847-330-3898

Name of Reviewer: John W. Metcalfe, Ph.D.

Conclusion: Not Approvable.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: New 505(b)(2) Application.

2. SUBMISSION PROVIDES FOR: A new drug product.

3. MANUFACTURING SITE:
APP Pharmaceuticals, LLC
Road 140 Km. 64.4
Barceloneta, Puerto Rico 00617

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:
- Sterile solution in (b) (4) glass vial (2.5 mL fill).
- Intravenous Injection.
- 100 mg/mL.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Anti-coagulant.

B. SUPPORTING/RELATED DOCUMENTS:
- Microbiology Review of ANDA 65,372 (dated 13 June 2007).

C. REMARKS:
The subject application is submitted electronically in the CTD format.

Reviewer's Comment
It is understood by this reviewer that the Barceloneta facility referenced in the subject submission for manufacture of the subject drug product closed during the summer of 2010 (after submission of the NDA). The subject review pertains to the manufacturing processes described in the NDA at the Barceloneta facility. If the applicant chooses to manufacture the subject drug product at an alternate facility, a microbiology review of the manufacturing processes and controls at the proposed facility will need to be performed.

File Name: N201811R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – NDA 201,811/N-000 is NOT approvable. Reference is made to this reviewer's comment on Page 20 of this review.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – Not applicable.

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology - (b) (4)

B. Brief Description of Microbiology Deficiencies –

- The application states that there are vials from two different manufacturers which may be used in the manufacture of the subject drug product. Container closure integrity studies were performed using one of these vials, but not both of them.
- The drug product manufacturing facility closed during the drug product review cycle. At the time of this writing, an alternate manufacturing facility has not been identified.
- The labeling information regarding storage of the final product needs to be modified to reflect the microbiological studies which were performed in support of the product label.

C. Assessment of Risk Due to Microbiology Deficiencies – Taken together, these microbiology deficiencies present a significant risk to the microbiological quality of the subject drug product.

III. Administrative

A. Reviewer's Signature _____
John W. Metcalfe, Ph.D.

B. Endorsement Block_____
Bryan S. Riley, Ph.D.

C. CC Block
N/A

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/s/

JOHN W METCALFE
01/13/2011
The subject submission is not approvable from the standpoint of product quality microbiology.

BRYAN S RILEY
01/13/2011
I concur.