

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201849Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

Product Quality Microbiology Review

15 August 2012

NDA: 201849/N-000

Drug Product Name

Proprietary:

N/A.

Non-proprietary:

Glucagon for Injection.

Review Number:

1.

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
30 NOV 2011	30 NOV 2011	06 DEC 2011	07 DEC 2011
31 MAY 2012	31 MAY 2012	N/A	N/A

Applicant/Sponsor

Name:

APP Pharmaceuticals, LLC.

Address:

1501 East Woodfield Rd.

Suite 300 E

Schaumburg, IL 60173

Representative:

Heidi Guzalo

Telephone:

847-517-5772

Name of Reviewer:

John W. Metcalfe, Ph.D.

Conclusion:

Recommend approval.

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** A 505(b)(2) Resubmission.
 2. **SUBMISSION PROVIDES FOR:** Response to Refuse to File Letter.
 3. **MANUFACTURING SITE:**
APP Pharmaceuticals, LLC.
2020 Ruby St.
Melrose Park, IL 60160
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - Lyophilized powder in 3 mL glass vial.
 - Intravenous and intramuscular injection.
 - 1 mg/vial.
 5. **METHOD(S) OF STERILIZATION:** [REDACTED] (b) (4)
 6. **PHARMACOLOGICAL CATEGORY:** The subject drug product is indicated during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract.

B. **SUPPORTING/RELATED DOCUMENTS:**

- Microbiology Review of [REDACTED] (b) (4)
- Microbiology Review of ANDA 65372; dated 13 June 2007.

- C. **REMARKS:** The application is submitted electronically in the CTD format. The original submission (dated 05 October 2010) was not reviewed by this reviewer since it received a Refuse to File decision on 03 December 2010 on the basis of non-clinical, regulatory, CMC, clinical pharmacology and clinical issues.

A Microbiology Information Request was forwarded to the applicant on 23 May 2012 by the OND Project Manager. Following is the request:

Microbiology Reviewer Comment #1.

We note that your drug product manufacturing process includes [REDACTED] (b) (4)

- *Provide a commitment to perform bioburden sampling* [REDACTED] (b) (4)
[REDACTED] *You may continue to perform the*
bioburden sampling step [REDACTED] (b) (4)

(b) (4) if you so desire.

Microbiology Reviewer Comment #2.

Reference is made to the bacterial endotoxins inhibition/enhancement verification study provided in Module 3.2.P.5.3.1.4. We note that only one product lot (R107-002) was tested, and that a statement of endotoxin recovery confirmation (rather than a data set from this testing) was provided in the NDA.

- Provide data sets from bacterial endotoxins inhibition/enhancement verification testing of three lots of the subject drug product.

A response to this request for information was submitted to the NDA on 31 May 2012. The responses are summarized and reviewed in appropriate sections of this review.

File Name: N201849R1.doc

Executive Summary

I. Recommendations

- A. **Recommendation on Approvability** – NDA 201849/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

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/s/

JOHN W METCALFE
08/15/2012

STEPHEN E LANGILLE
08/15/2012

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 201849 **Applicant:** APP Pharmaceuticals LLC **Letter Date:** 30 November 2011

Drug Name: Glucagon **NDA Type:** 505 (b)(2). **Stamp Date:** 30 November 2011
for Injection.

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		Module 3.2.P. The application is submitted in the eCTD format.
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		Module 3.2.P.3.3.
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		Module 3.2.P.3.3.
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	X		Module 3.2.P.2. (for CCI). The product is not preserved.
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		Module 3.2.P.5.1.
7	Has the applicant submitted the results of analytical method verification studies?	X		Module 3.2.P.5.3.1.4.
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?			This reviewer is unaware of any pre-submission information related to the subject submission.
9	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: The subject drug product consists of a lyophilized powder in glass vial ^{(b) (4)}

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

January 3, 2012

Date

Bryan S. Riley, Ph.D.
Senior Microbiology Reviewer, CDER/OPS/NDMS.

Date

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/s/

JOHN W METCALFE
01/03/2012

BRYAN S RILEY
01/03/2012
I concur.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 201-849/N-000 **Applicant:** APP Pharmaceuticals **Letter Date:** 05 October 2010

Drug Name: Glucagon for Injection **NDA Type:** 505(b)(2) **Stamp Date:** 05 October 2010

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		The NDA is submitted electronically in the CTD format.
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		Module 3.2.P.3.3.
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		Module 3.2.P.3.5.
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	X		The product is not preserved. CCI studies are provided in Module 3.2.P.2.5.
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		Module 3.2.P.5.
7	Has the applicant submitted the results of analytical method verification studies?	X		Module 3.2.P.5.3.1.4.
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?			This reviewer is not aware of any special/critical studies/data requested prior to submission of the NDA.
9	Is this NDA fileable? If not, then describe why.	X		

Additional Comments:

The drug product consists of a (b) (4) lyophilized powder. (b) (4)

[Redacted]

19 November 2010

John W. Metcalfe, Ph.D.

Date

Bryan S. Riley, Ph.D.

Date

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/s/

JOHN W METCALFE
11/23/2010

BRYAN S RILEY
11/23/2010
I concur.