CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761025Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

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:	August 28, 2015
To:	Administrative File, STN 761025/0
From:	Reyes Candau-Chacon, PhD. Reviewer, CDER/OPQ/OPF/DMA/Branch IV
Through:	Patricia Hughes, Ph.D., Acting Branch Chief, CDER/OPQ/OPF/DMA/Branch IV
Subject:	Addendum to New Biologic License Application (BLA) to address microbial quality limits (b) (4)
US License:	2006
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.
Facilities:	Boehringer Ingelheim Pharma GmbH & Co KG, Birkendorfer Strasse 65, 88397 Biberach / Riss, Germany (FEI 3007748866)
Product:	Praxbind (Idarucizumab)
Dosage:	Sterile solution for intravenous injection in two (2) separate 50 mL vials each containing 2.5 g Idarucizumab.
Indication:	Rapid reversal of anticoagulant effects of dabigatran
Due date:	October 19, 2015

Recommendation for Approvability: The drug substance part of BLA 761025 was reviewed from a microbial control and microbiology product quality perspective and is recommended for approval.

Summary

This addendum provides the review of Boehringer Ingelheim's amendment 0013 submitted on July 29, 2015 in response to an Information Request sent by the Agency on July 23, 2015. The amendment addresses bioburden and endotoxin limits (b) (4), endotoxin limits of (b) (4) and submission of information from pending qualification reports.

FDA Information Request sent on July 23, 2015, Question 1

Please clarify for the (b) (4)

BI Response in amendment 0013
BI indicates that [redacted]

Satisfactory

FDA Information Request sent on July 23, 2015, Question 2
Indicate when the [redacted] qualification report using samples from two additional batches will be submitted to the Agency

BI Response in amendment 0013
BI indicates that the qualification report will be submitted in the next Annual Report.

Satisfactory

FDA Information Request sent on July 23, 2015, Question 3
Submit endotoxin limits of [redacted] purification steps.

BI Response in amendment 0013
BI submitted the following table with the endotoxin limits for the requested [redacted]:

Process step / [redacted]	Bacterial Endotoxin process limit [EU/mL]
[redacted]	

Satisfactory

FDA Information Request sent on July 23, 2015, Question 4
Indicate when the study report for the maximum hold times of [redacted] from microbiology perspective will be submitted to the Agency.

BI Response in amendment 0013
BI indicates that the maximum hold time validation report will be conducted in the next campaign and submitted in the following Annual Report.

Satisfactory

FDA Information Request sent on July 23, 2015, Question 5

It is noted that due to your current (b) (4)

BI Response in amendment 0013

BI indicates that the acceptance criteria for the (b) (4)

Satisfactory

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Maria D. Candauchacon -S

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Reyes Candau-Chacon, Primary Reviewer

Patricia F. Hughestroost -S

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Patricia Hughes, Acting Branch Chief

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
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Date: August 28, 2015
To: Administrative File, STN 761025/0
From: Reyes Candau-Chacon, PhD. Reviewer, CDER/OPQ/OPF/DMA/Branch IV
Through: Patricia Hughes, Ph.D., Acting Branch Chief, CDER/OPQ/OPF/DMA/Branch IV
Subject: Addendum to New Biologic License Application (BLA) to address microbial quality limits (b) (4)
US License: 2006
Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.
Facilities: Boehringer Ingelheim Pharma GmbH & Co KG, Birkendorfer Strasse 65, 88397 Biberach / Riss, Germany (FEI 3007748866)
Product: Praxbind (Idarucizumab)
Dosage: Sterile solution for intravenous injection in two (2) separate 50 mL vials each containing 2.5 g Idarucizumab.
Indication: Rapid reversal of anticoagulant effects of dabigatran
Due date: October 19, 2015

Recommendation for Approvability: The drug substance part of BLA 761025 was reviewed from a microbial control and microbiology product quality perspective.

Summary

This addendum provides the review of Boehringer Ingelheim's amendment 0013 submitted on July 29, 2015 in response to an Information Request sent by the Agency on July 23, 2015. The amendment addresses bioburden and endotoxin limits (b) (4), endotoxin limits of (b) (4), and submission of information from pending qualification reports.

FDA Information Request sent on July 23, 2015, Question 1
Please clarify for the (b) (4)

BI Response in amendment 0013
BI indicates that (b) (4)

Satisfactory

FDA Information Request sent on July 23, 2015, Question 2
Indicate when the (b) (4) qualification report using samples from two additional batches will be submitted to the Agency

BI Response in amendment 0013
BI indicates that the qualification report will be submitted in the next Annual Report.

Satisfactory

FDA Information Request sent on July 23, 2015, Question 3
Submit endotoxin limits of (b) (4) purification steps.

BI Response in amendment 0013
BI submitted the following table with the endotoxin limits for the requested (b) (4):

Process step / (b) (4)	Bacterial Endotoxin process limit [EU/mL]
(b) (4)	

(b) (4)

Satisfactory

FDA Information Request sent on July 23, 2015, Question 4
Indicate when the study report for the maximum hold times of (b) (4) from microbiology perspective will be submitted to the Agency.

BI Response in amendment 0013
BI indicates that the maximum hold time validation report will be conducted in the next campaign and submitted in the following Annual Report.

Satisfactory

FDA Information Request sent on July 23, 2015, Question 5

It is noted that due to your current (b) (4)

BI Response in amendment 0013

BI indicates that the acceptance criteria for the (b) (4)

Satisfactory

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Reyes Candau-Chacon, Primary Reviewer

Patricia F. Hughestroost -S

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Patricia Hughes, Acting Branch Chief

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

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

Date: **August 11, 2015**
To: Administrative File, STN 761025
From: Candace Gomez-Broughton, Ph.D., CDER/OPQ/OPF/DMA
Endorsed: Patricia Hughes, Ph.D. CDER/OPQ/OPF/DMA
Subject: Original Biologic License Application
US License: 2006
Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.
Facility: DP: Boehringer Ingelheim Pharma GMbH & Co KG Biberach, Germany
FEI: 3007748866
Product: Praxbind™ (idarucizumab)
Dosage: solution for injection or infusion (50 mg/mL)
Indication: Rapid reversal of anticoagulant effect of dabigatran
Due date: October 19, 2015

Recommendation: The drug product section of the BLA is recommended for approval from a microbiology product quality perspective.

INTRODUCTION

This review covers the product quality microbiology of the drug product as presented in BLA section 3.2.P. The product quality microbiology review for the DS was completed by Reyes Candau-Chacon, Ph.D. in a separate memo.

DRUG PRODUCT QUALITY MICROBIOLOGY ASSESSMENT

Amendments Reviewed For Drug Product Quality Microbiology

- SDN 0005 – response to information request sent 10-Jul-2015
- SDN0018 – updates documents in the Module 3 as described in responses to prior information requests

P Drug Product

P.1 Description and Composition of the Drug Product

The idarucizumab drug product is a preservative-free solution presented in 50 mL Type 1 glass vials at a concentration of 50 mg/mL. The formulation consists of 25 mM sodium acetate/acetate, 220 mM sorbitol and 0.2 g/L (0.02 w%) polysorbate 20 at pH 5.5.

P.2 Pharmaceutical Development

Idarucizumab drug product manufacturing follows [redacted (b) (4)]

A risk-based approach was used to design an efficient commercial manufacturing process with effective controls. Process parameters and their impact on critical quality attributes (CQAs) were investigated to define proven acceptable ranges to ensure consistent drug product quality. Process development studies were completed at the drug product manufacturing facility in Biberach, Germany.

P.2.5 Microbiological Attributes

The idarucizumab drug product is filled [redacted (b) (4)]. Sterility and bacterial endotoxins are measured at release as discussed in Section P.5.1 Specification. In addition, sterility assurance is maintained by using [redacted (b) (4)].

P.2.5.1 Container Closure Integrity Test

Vacuum decay is the method used to assess container closure integrity (CCI). The vacuum decay method has a limit of detection of [redacted (b) (4)] microns. The test was completed on four validation lots to confirm CCI. [redacted (b) (4)] vials from each lot were tested. The results confirm that container closure integrity is maintained for the drug product configuration. CCI testing is completed as a part of the stability program (Section P.8.3.2).

P.3 Manufacture

P.3.1 Manufacturers

The table below provides a list of idarucizumab drug product manufacturing sites and the operations that take place in each.

Facility	FEI	Operations
Boehringer Ingelheim Pharma GmbH & Co KG (Biberach)	3007748866	DP manufacturing, release, stability, labeling, secondary packaging
[redacted (b) (4)]		Stability testing
Boehringer Ingelheim Roxane, Inc. (Columbus, Ohio)	1510690	labeling, secondary packaging

Reviewer comment: Facilities are reviewed in a separate memo by the Division of Inspectional Assessment.

P.3.2 Batch Formula

The idarucizumab drug product is presented as a liquid for solution or infusion at a concentration of 50 mg/mL. The formulation consists of 25 mM sodium acetate/acetate, 220 mM sorbitol, and

0.2 g/L (0.02 w %) polysorbate 20 at pH 5.5.

The validated batch size for commercial production ranges from (b) (4) vials.

P.3.3 Description of Manufacturing Process and Process Controls

Idarucizumab drug product manufacturing process includes the following unit operations:

(b) (4)

(b) (4)

Reviewer Question: Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls, Table 4 "Idarucizumab (b) (4)" appears to summarize (b) (4). Please provide a description of the (b) (4) for the drug product manufacturing process.

Sponsor Response: The sponsor provided the overall maximum hold time for the drug product filling process at (b) (4) The normal operating range is (b) (4) and the maximum hold time (Proven Acceptable Range) is (b) (4). These durations have been covered by process validation studies and media simulations.

Reviewer Question: We acknowledged your protocols for validation (b) (4) that you have provided in your June 26, 2015 responses to the FDA. We also note that there is an (b) (4) (page 259 of your response). (b) (4)
Indicate if (b) (4) in the drug product manufacturing process. Any (b) (4) steps in the drug product manufacturing process should be clearly identified in section 3.2.P.3.3, including descriptions of the conditions under which (b) (4) would occur, (b) (4) etc. Adequate justification for these control parameters and timelines should be provided. Additionally, you should also identify in the BLA that successful results of the (b) (4) validation protocols will be submitted in an annual report.

Sponsor Response (Sequence 0015): (b) (4)

. Section 3.2.P.3.3 of the BLA was amended to indicate (b) (4) (SDN 0018).

SATISFACTORY

P.3.4 Control of Critical Steps and Intermediates
The in-process controls and corresponding acceptance criteria are summarized in the table below:

Process Step	In-Process Test	Limit
(b) (4)		

Analytical Procedures for Controls at Critical Steps
(b) (4)

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SATISFACTORY

P.8 Stability

P.8.1 Stability Summary and Conclusions

The stability program for drug product currently consists of 9 lots stored at the recommended storage condition (2-8°C), under accelerated (25°C/60% RH), and stress (40°C/75% RH) storage conditions. The stability program includes clinical lots, lots manufactured for primary stability, as well as process validation lots. The stability protocol includes testing through 48 months with optional testing at 60 months if the drug product meets specifications. The lots used in the stability program are listed in the table below.

DP Lot #	Date of Manufacture	Classification
207732	13-Dec-12	Primary Stability
207733	14-Dec-12	
306691	6-Nov-13	
306692	7-Nov-13	
306693	8-Nov-13	
307240	13-Nov-13	
E1739F06	30-Nov-13	Supportive Stability
E2739F01	15-Mar-12	
DAB-FTOX-01	29-Nov-11	

Based on the current stability data, the proposed shelf life is 30 months at 2-8°C for idarucizumab drug product.

P.8.2 Post-Approval Stability Protocol and Stability Commitment
Container closure integrity will be performed annually using the vacuum decay method. Six primary stability lots will be tested through the proposed shelf life of 30 months.

Long-term stability testing will be performed on one commercial lot of idarucizumab on an annual basis. Results will be reported to the Agency in the BLA Annual Report. Any lot that fails specification will be withdrawn from the market. Single deviations that affect the safety and efficacy of the drug product will be discussed with the Agency. A change or deterioration in the distributed drug product will be reported to the Agency.

P.8.3 Stability Data
Primary Stability Data
Stability results have been collected for 24 months at long-term storage conditions for two primary stability lots and for 12 months for four lots. Also, 12 months of data has been compiled for five lots held in accelerated conditions.

Stability data is provided although it is not part of the commercial stability specifications. Sterility was determined at the beginning, yearly, and end of the stability study for lots kept at long term storage conditions. Container closure integrity is assessed annually and at the end of the stability study for lots kept at long term storage conditions. All acceptance criteria were met.

Stress Stability Data
Drug product lot 207732 placed under stressed (freeze-thaw) conditions was tested for sterility and container closure integrity. (b) (4) Sterility and container closure integrity results met the acceptance criteria (no growth/pass) for all three freeze-thaw cycles.

Reviewer comment: The current stability data from long term, accelerated, and stressed storage conditions support the proposed 30 month shelf from a microbiological perspective.

CONCLUSION

I. The drug product section of BLA is recommended for approval from a microbial control and microbiology product quality perspective. No approvability issues have been identified and the review of the pending responses to information requests will be included as an addendum to this review.

II. Information and data in this BLA not related to microbial control of the drug product should be reviewed by the OBP reviewer.

III. Refer to Panorama for GMP status of the relevant facilities.

FDA Information Request for STN 761025/0 Microbial Quality- Drug Product

P.3.3 Description of Manufacturing Process and Process Controls

Table 4 "Idarucizumab [redacted]" appears to summarize [redacted]. Please provide a description of the [redacted] for the drug product manufacturing process.

P.3.4 Control of Critical Steps and Intermediates

Please amend this BLA section to include descriptions of the analytical methods used to measure [redacted] bioburden and endotoxin.

P.3.5 Process Validation and/or Evaluation

1. Provide the filling duration for each validation run. Specifically, the duration from the [redacted]. Include definitions of the start and end time points.

2. Please submit the study reports for the [redacted] studies completed during the initial qualification studies for [redacted]. Please include the source of the endotoxin used in the study.

3. With regard to media fill, provide the dates for the current media fill data submitted in the BLA (Batches 301033, 305591, 401000, and 406043).

4. Define the start and end time for the fill durations used during media fills.

5. Provide actions taken in the event of a media fill failure.

6. With regard to the transport validation studies, please describe the monitoring points at which temperature data was collected.

7. Provide a description and/or a diagram showing the location of the [redacted].

8. Provide acceptance criteria for the transport validation studies.

FDA Information Request for STN 761025/0 Microbial Quality- Drug Product

P.3.3 Description of Manufacturing Process and Process Controls

We acknowledged your protocols for validation of [redacted] that you have provided in your June 26, 2015 responses to the FDA. We also note that there is an [redacted] (page 259 of your response). [redacted]. Indicate if [redacted] in the drug product manufacturing process.

Any [redacted] steps in the drug product manufacturing process should be clearly identified in section 3.2.P.3.3, including descriptions of the conditions under which [redacted] would occur, [redacted], etc. Adequate justification for these control parameters and timelines should be provided. Additionally, you should also identify in the BLA that successful results of the [redacted] validation protocols will be submitted in an annual report.

P.3.5 Process Validation and/or Evaluation

1. Submit the [redacted] microbial retention study report completed by [redacted]. The report should include controls, acceptance criteria, incubation conditions [redacted], and growth promotion ability of growth media.

2. Submit the validation report for the [redacted] integrity test. Be sure to include the following information:

   a. [redacted]

   b.

   c.

SIGNATURES

Candace Y. Gomez-broughton -S

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Patricia F. Hughestroost -S

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DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

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Date:	July 19, 2015
To:	Administrative File, STN 761025/0
From:	Reyes Candau-Chacon, PhD. Reviewer, CDER/OPQ/OPF/DMA/Branch IV
Through:	Patricia Hughes, Ph.D., Acting Branch Chief, CDER/OPQ/OPF/DMA/Branch IV
Subject:	New Biologic License Application (BLA)
US License:	2006
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.
Facilities:	Boehringer Ingelheim Pharma GmbH & Co KG, Birkendorfer Strasse 65, 88397 Biberach / Riss, Germany (FEI 3007748866)
Product:	Praxbind (Idarucizumab)
Dosage:	Sterile solution for intravenous injection in two (2) separate 50 mL vials each containing 2.5 g Idarucizumab.
Indication:	Rapid reversal of anticoagulant effects of dabigatran
Due date:	October 19, 2015

Recommendation for Approvability: The drug substance part of BLA 761025 was reviewed from a microbial control and microbiology product quality perspective. No approvability issues have been identified at this point and the review of a pending information request will be included as an addendum to this review.

Review Summary

Boehringer Ingelheim has submitted BLA 761025 to license idarucizumab drug substance and drug product and their manufacturing processes.

BLA 761025 was submitted in eCTD as a rolling BLA; the original application was submitted on December 22, 2014 and contained modules 1, 2, and 4; modules 3 and 5 were submitted on February 19, 2015 in amendment 0001. This review contains the assessment of the manufacturing process of idarucizumab bulk drug substance from a microbiological quality perspective. For review of drug product aspects of the application, please see the review by Dr. Candace Gomez-Broughton.

Amendments Reviewed for Drug Substance Quality

Information Request date	Question numbers	Amendment sequence	Amendment date
May 14, 2015	1 to 9	0007	June 4, 2015
June 15, 2015	1a, 1b, 2f, 2j, 2i, 3a	0009	June 26, 2015
July 15, 2015	2f, 3a	0012	July 17, 2015

Review Narrative

S DRUG SUBSTANCE

S.1 General Information

Idarucizumab is a humanized Fab molecule derived from a murine IgG1 isotype antibody. Idarucizumab specifically binds to dabigatran with a higher affinity than that of thrombin to reverse the anticoagulatory effect of dabigatran.

SATISFACTORY

S.2 Manufacture

S.2.1 Manufacturer(s)

The following facilities are used for the manufacture, release testing, and stability testing of idarucizumab drug substance:

- Boehringer Ingelheim Pharma GmbH & Co KG, Birkendorfer Strasse 65, 88397 Biberach / Riss, Germany; Drug substance manufacture, DS in-process release and stability testing
  FEI 3007748866

(b) (4)

[redacted]

Reviewer comments:

Refer to Panorama for the compliance status of all the relevant facilities.

S.2.2 Description of the Manufacturing Process and Process Controls

(b) (4)

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Reviewer Comments:
Microbial quality results of stability samples are not necessarily representative of microbial quality of drug substance (b) (4) (b) (4) *BDS stability is not required from a microbial quality point of view and is deferred to OBP.*

SATISFACTORY

Environmental Assessment
A categorical exclusion for an action on an application for marketing approval of a biological product for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment is claimed under 21 CFR 25.31(c).

cGMP Status
Refer to Panorama for cGMP status of the relevant facilities.

Conclusion

I. The drug substance part of BLA 761025 was reviewed from a microbial control and microbiology product quality perspective. No approvability issues have been identified at this point and the review of a pending information request will be included as an addendum to this review.

II. Information and data in this BLA not related to microbial control of the drug substance should be reviewed by an OBP reviewer.

III. Refer to Panorama for GMP status of the relevant facilities.

FDA Information Request for STN 761025/0 Microbial Quality – Drug Substance

1. **Description of the Manufacturing Process and Process Controls**

(b) (4)

2. **Control of Critical Steps and Intermediates**

(b) (4)

3. **Process Validation and/or Evaluation** – PPQ batches

(b) (4)

4. **Process Validation and/or Evaluation – Transportation**

(b) (4)

(b) (4)

5. **Specifications**
   Indicate if bioburden results are calculated as the sum of TAMC + TYMC.

6. **Analytical Procedures**
   Provide a description of the drug substance bioburden and endotoxin methods.

7. **Validation of Analytical Procedures**

(b) (4)

8. **Batch Analyses**
   Justify endotoxin results of batches 10810007, 10810007, 10810009 and 10810010 of (b) (4)

9. **Container Closure System**

(b) (4)

FDA Information Request for STN 761025/0 Microbial Quality – Drug Substance
In reference to the information submitted on Jun 4, 2015 in response to FDA's information request of May 14, 2015, we have the following requests for clarification and additional information:

a. With regards to your response to question 1.a, clarify if samples "(b) (4)

b. (b) (4)
   Please provide data justifying the new (b) (4) hold times.

c. With regard to your response to question 2.f, qualify bioburden (b) (4) samples using two additional runs.

d. With regard to your response to question 2.i, justify how (b) (4)
   .

e. With regard to your response to question 2.j, include (b) (4) .

f. With regard to your response to question 3.a. (b) (4) .

g. Clarify if the (b) (4) used for batch 10810002 are identical to the (b) (4) used for batch 10810000 and if batch 10810000 was (b) (4)

FDA Information Request for STN 761025/0 Microbial Quality – Drug Substance
In reference to the information submitted on Jun 26, 2015 in response to FDA's information request of June 14, 2015, we have the following requests for clarification and additional information:

With regard to your response to question 1.d (from original question 2.i) submitted in amendment 0009, (b) (4)

With regard to your response to question 1.f (from original question 3.a) submitted in amendment 0009, (b) (4)

FDA Information Request for STN 761025/0 Microbial Quality – Drug Substance
(The responses to this information request will be included as an addendum to the drug substance microbial quality portion of the BLA.)

1. Please clarify [redacted (b) (4)]
2. Indicate when the [redacted (b) (4)] qualification report using samples from two additional batches will be submitted to the Agency
3. Submit endotoxin limits of [redacted (b) (4)] purification steps
4. Indicate when the study report for the [redacted (b) (4)] from microbiology perspective will be submitted to the Agency.
5. It is noted that due to your current [redacted (b) (4)]

Study reports for the qualification of [redacted (b) (4)] method and hold time validation can be submitted in the next Annual Report.

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Maria D. Candauchacon -S

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Reyes Candau-Chacon, Primary Reviewer

Bo Chi -A

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Bo Chi, for Patricia Hughes, Acting Branch Chief