CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761025Orig1s000

CHEMISTRY REVIEW(S)

First Approval for Indication

Recommendation: Approve

BLA 761025
September 1, 2015

Drug Name/Dosage Form	**Praxbind (Idarucizumab) solution for injection**
Strength/Potency	**50 mg/ml**
Route of Administration	**Intravenous**
Rx/OTC Dispensed	**Rx**
Indication	**Emergency reversal of dabigatran**
Applicant/Sponsor	**Boehringer Ingelheim**
US agent, if applicable	**NA**

a. Names
   i. Proprietary Name: Praxbind
   ii. Trade Name: Praxbind
   iii. Non-Proprietary/USAN: idarucizumab
   iv. INN Name: idarucizumab
   v. Other: BI 655075
   vi. OBP systematic name: MABFRAG HUMANIZED (IGG1) ANTI_dabigatran

b. Pharmacologic category: Therapeutic humanized murine Fab fragment.

Product Overview

Praxbind (idarucizumab) is a humanized murine Fab fragment produced in CHO cells. Idarucizumab binds to the thrombin inhibitor dabigatran and in doing so, inhibits the anticoagulatory effect of dabigatran. The binding affinity of idarucizumab to dabigatran is approximately 300-fold higher than the binding affinity of dabigatran for thrombin. Praxbind is proposed to be used in patients treated with dabigatran, when rapid reversal of the anticoagulant effects of dabigatran are necessary in the case of emergency surgery or urgent procedures and/or for life threatening or uncontrolled bleeding.

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
OBP- Drug Substance	**Tura C. Camilli**	**Division of Biotechnology Review and Research I**
OBP- Assay validation and Immunogencity	**Lixin Xu**	**Division of Biotechnology Review and Research IV**
OBP- Drug Product	**Frederick Mills**	**Division of Biotechnology Review and Research IV**
Microbiology- Drug Substance	**Reyes Candau-Chacon**	**Division of Microbiology Assessment**
Microbiology- Drug Product	**Candace Gomez-Broughton**	**Division of Microbiology Assessment**
Facilities- Drug Substance	**Wayne Seifert**	**Division of Inspectional Assessment**
Facilities- Drug Product	**Don Obenhuber**	**Division of Inspectional Assessment**
Facilities- Team Lead	**Steven Fong**	**Division of Inspectional Assessment**
Microbiology- Team Lead	**Patricia Hughes**	**Division of Microbiology Assessment**
Business Regulatory Process Manager	**Melinda Bauerlein**	**OPRO**
Application Technical Lead	**Chana Fuchs**	**Division of Biotechnology Review and Research IV**

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	**Alycia Anderson**	OHOP/Division of Hematology Products
Cross-disciplinary Team Lead	**Kathy Robie Suh**	OHOP/Division of Hematology Products
Medical Officer	**Andrew Dmytrijuk**	OHOP/Division of Hematology Products
Pharm/Tox	**Emily Place**	OHOP/Divison of Hematology Oncology
Clinical Pharmacology	**Martina Sahre**	OCP/Division of clinical pharmacology I
Statistics	**Yuan Li Shen**	OB/Division of Biometrics V

Quality Review Team – Signature Page

DISCIPLINE	REVIEWER	BRANCH/DIVISION	e-Signature
OBP - Drug Substance	Tura C. Camilli	Division of Biotechnology Review and Research I	Tura C. Camilli -S Digitally signed by Tura C. Camilli -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0013464266, cn=Tura C. Camilli -S Date: 2015.10.14 16:52:05 -04'00'
OBP - Assays and Immunogenicity	Lixin Xu	Division of Biotechnology Review and Research IV	Lixin Xu -S Digitally signed by Lixin Xu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lixin Xu -S, 0.9.2342.19200300.100.1.1=1300378659 Date: 2015.10.14 16:37:28 -04'00'
OBP - Drug Product	Frederick Mills	Division of Biotechnology Review and Research IV	Frederick C. Mills -S Digitally signed by Frederick C. Mills -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000737256, cn=Frederick C. Mills -S Date: 2015.10.14 17:00:58 -04'00'
Microbiology- Drug Substance	Maria Candau-Chacon	Division of Microbiology Assessment	Maria D. Candauchacon -S Digitally signed by Maria D. Candauchacon -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000639745, cn=Maria D. Candauchacon -S Date: 2015.10.15 08:06:56 -04'00'
Microbiology - Drug Product	Candace Gomez-Broughton	Division of Microbiology Assessment	Candace Y. Gomez-broughton -S Digitally signed by Candace Y. Gomez-broughton -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000640207, cn=Candace Y. Gomez-broughton -S Date: 2015.10.14 17:13:46 -04'00'
Facilities - Drug Substance	Wayne Seifert	Division of Inspectional Assessment	Wayne E. Seifert -S Digitally signed by Wayne E. Seifert -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001593284, cn=Wayne E. Seifert -S Date: 2015.10.14 16:29 44 -04'00'
Facilities - Drug Product	Don Obenhuber	Division of Inspectional Assessment	Donald Obenhuber -A Digitally signed by Donald Obenhuber -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000330000, cn=Donald Obenhuber -A Date: 2015.10.15 06:59:29 -04'00'
Microbiology - Team Lead	Patricia Hughes	Division of Microbiology Assessment	Patricia F. Hughestroost -S Digitally signed by Patricia F Hughestroost S DN: c US o U S Government ou HHS ou FDA ou People 0 9 2342 19200300 100 1 1 1300096547 cn Patricia F Hughestroost S Date: 2015 10 15 07:25:28 04'00'
Facilities - Team Lead	Steven Fong	Division of Inspectional Assessment	Steven Fong -S Digitally signed by Steven Fong -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Steven Fong -S, 0.9.2342.19200300.100.1.1=2000287433 Date: 2015.10.14 20:44:34 -04'00'
Branch Chief	Michele Dougherty	Division of Biotechnology Review and Research IV	Michele Dougherty -S Digitally signed by Michele Dougherty -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0010556865, cn=Michele Dougherty -S Date: 2015.10.14 16:45:00 -04'00'
Application Technical Lead	Chana Fuchs	Division of Biotechnology Review and Research IV	Chana Fuchs -S Digitally signed by Chana Fuchs S DN: c US o U S Government ou HHS ou FDA ou People cn Chana Fuchs S 0 9 2342 19200300 100 1 1 2000601863 Date: 2015 10 14 16:21:13 04'00'

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(a)

2. RELATED/SUPPORTING DOCUMENTS:

A. Submissions Reviewed

SUBMISSION(S) REVIEWED	DOCUMENT DATE
STN 761025/0001	02/19/2015
STN 761025/0002	04/02/2015
STN 761025/0003	04/07/2015
STN 761025/0006	05/13/2015
STN 761025/0008	05/28/2015
STN 761025/0007	06/04/2015
STN 761025/0009	06/26/2015
STN 761025/0005	07/15/2015
STN 761025/0012	07/17/2015
STN 761025/0013	07/17/2015
STN 761025/0014	08/12/2015
STN 761025/0015	07/31/2015
STN 761025/0017	08/12/2015
STN 761025/0018	08/12/2015
STN 761025/0019	08/19/2015
STN 761025/0021	09/22/2015
STN 761025/0023	10/09/2015

B. DMFs:

Cross reference letters were included in the BLA for the following DMFs:

1. DMF (b) (4) : Type Ill DMF - from (b) (4). The BLA cross referenced this DMF for:

   Glass tubing/vials - Date Of Submission: (b) (4) This DMF was not reviewed for the purpose of this BLA because sufficient information was submitted in the BLA regarding the vials, extractables and leachables, and vial/product interaction.

2. DMF (b) (4) : Type Ill DMF from (b) (4). The BLA cross references this DMF for:

   (b) (4)

   This DMF was not reviewed for the purpose of this BLA because sufficient information was submitted in the BLA regarding the stopper, including extractables and leachables, and for data on product interaction with the container closure system.

C. Other Documents: None

3. CONSULTS: None

Integrated Review

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA STN 761025 for Praxbind (idarucizumab) manufactured by Boerhinger Ingelheim Pharmaceuticals, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Praxbind (idarucizumab) is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

1. Benefit/Risk Considerations:

Praxbind is proposed to be used in patients treated with dabigatran, when rapid reversal of the anticoagulant effects of dabigatran are necessary in the case of emergency surgery or urgent procedures and/or for life threatening or uncontrolled bleeding. Therefore, Praxbind may address currently unmet medical needs. Based on assessment of the manufacturing process and controls, and GMP compliance of the manufacturing facilities, the drug substance and drug product manufacturing processes are well controlled and should consistently deliver DS of desired quality.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Quality Assessments

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1, below, is a summary of critical quality attributes and their control strategy that are relevant to both drug substance (DS) and drug product (DP). CQAs for the formulated DS are identified by the superscript "[a]" and CQAs for DP are identified by the superscript "[b]". For additional information see Appendix A for the Drug Substance and Appendix B for the Drug Product Quality Reviews: OBP Assessment, Appendix C for the Drug Substance and Appendix D for the Drug Product Quality Reviews: Microbial Assessment

2 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

B. Drug Substance: Idarucizumab Quality Summary

CQA Identification, Risk and Lifecycle Knowledge Management
Drug substance critical quality attributes and their control strategy are identified with a superscript "a" in table 1 above. For additional information see Appendix A for the Drug Substance Quality Review: OBP Assessment, and Appendix C Drug Substance Microbiology Review: Division of Microbiology Assessment.

1. Description

Idarucizumab is a humanized murine Fab fragment that was generated by standard monoclonal antibody techniques and is expressed in Chinese Hamster Ovary (CHO) cells. (b) (4) [redacted] For additional information see Appendix A and Appendix C.

2. Mechanism of action
   Dabigatran acts as a thrombin inhibitor to reduce thrombotic events. Use of dabigatran, like other anticoagulant therapy, can be associated with uncontrolled bleeding, often during emergency situations. Idarucizumab binds specifically to dabigatran and in doing so, neutralizes dabigatran's anticoagulant effects. Idarucizumab has much higher affinity for dabigatran (Kd= 2.1pM) than dabigatran for thrombin (Kd=0.7nM), thereby ensuring that any dabigatran will become bound by free idarucizumab.
   For additional information see Appendix A.

3. Potency Assay
   Potency is defined as the percent activity relative to idarucizumab reference standard. There are two potency assays used to assess idarucizumab binding of dabigatran. The first potency assay is a binding assay that measures binding activity of idarucizumab to dabigatran by surface plasmon resonance. The second potency assay is a thrombin clotting assay that measures the increase in turbidity caused by fibrin clots when idarucizumab is added to samples containing dabigatran. This assay provides a direct measurement of idarucizumab's ability to reverse the inhibition of thrombin clotting by pradaxa. The potency assays are suitable since they are highly relevant to the idarucizumab mechanism-of-action. For additional information see Appendix A.

4. Reference material(s)
   A two tiered reference standard system was developed consistent with ICHQ6B recommendations. The primary reference standard is not used for routine testing but rather to anchor the potency, purity, and other quality attributes for future reference standards and to assess stability of the working reference standard. The working reference standard is used for routine testing. The primary and working reference standards were derived from [redacted] (b) (4), and were used for DS and DP released during the phase III clinical study. The

reference standards were rigorously characterized by both release testing and additional biochemical characterization. The reference standards are suitable for their intended uses in idarucizumab testing. For additional information see Appendix A.

5. Manufacturing process summary

(b) (4)

(b) (4)

The overall control strategy combines control of raw materials, facilities and equipment, manufacturing process, and adventitious agents. The combined control strategies with in-process and release testing ensure process consistency and a drug substance with appropriate quality attributes that is free of adventitious agents.

For additional information see Appendix A and Appendix C.

6. Container closure system:
The drug substance container closure system is (b) (4) For additional information see Appendix A.

7. Dating period and storage conditions:
The sponsor conducted real time, accelerated, and stressed stability studies to support a dating period of (b) (4) months when stored at (b) (4) °C or (b) months when stroed at (b) (4) °C. (b) (4) For additional information see Appendix A.

A post-approval stability protocol was included to support extension of expiration dating based on additional stability data.

C. Drug Product: Praxbind Quality Summary

A summary of the the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes are identified with a superscript "[b]" in table 1 above. For additional information see Appendix B for the Drug Substance Quality Review: OBP Assessment, and Appendix D Drug Substance Microbiology Review: Division of Microbiology Assessment

a. Potency and Strength
Potency is defined as the percent activity relative to idarucizumab reference standard. The potency assays for DP are the same as those described in the DS section B3 of this memo. Praxbind will be available at a strength of 50mg/ml.

b. Summary of Product Design
Idarucizumab will be available in in a pack of 2 single use vials each containing 2.5 g/50 mL idarucizumab. Each 2-pack is designed to deliver the full dose of 5g of idarucizumab.

c. Excipients
Sodium acetate trihydrate, sorbitol, polysorbate 20, glacial acetic acid. The excipients used in manufacturing are compendial quality grade and acceptable for use. None of the excipients are of human or animal origin and therefore are of little risk for viral or TSE contamination. The drug product is preservative free. For additional information see Appendix A and Appendix B.

d. Reference material(s)
There is no drug product specific reference material. The primary and working reference materials are drug substance. Please see section B4 of this memo for information on the reference materials used in control of DP.

e. Manufacturing Process
The drug product manufacturing process can (b) (4)

The control strategy includes (b) (4)

[redacted] (b) (4) Process validation studies included manufacture of [redacted] (b) (4)

Sterility is measured at release, and sterility assurance is maintained [redacted] (b) (4) Container Closure Integrity was assessed as part of validation and is included in the DP stability program. For additional information see Appendix D.

f. Container Closure System
The primary container closure system for Praxbind is a single-use 50 mL clear type 1 glass vial stoppered with a [redacted] (b) (4) rubber stopper and sealed with [redacted] (b) (4).
The drug product CCS components are suitable for parenteral products with minimal leaching and with minimal degradation for the duration of the dating period when stored at 2-8°C and in the dark.

g. Expiration Date & Storage Conditions
The sponsor conducted real time, accelerated, and stressed stability studies on drug product to support a dating period of 30 months when stored at 2-8°C in the dark.

h. List of co-packaged components
None (other than package Insert)

D. Novel Approaches/Precedents N/A

E. Any Special Product Quality Labeling Recommendations

Store in a refrigerator at 2-8°C
Do note freeze
Do not shake
Protect from light

F. Establishment Information

OVERALL RECOMMENDATION: Approve					
FUNCTION	**SITE INFORMATIO**	**DUNS/F EI**	**PRELIMINARY ASSESSMENT**	**INSPECTIONAL OBSERVATIONS**	**FINAL RECOMMENDATIO**
DRUG SUBSTANCE					
• Cell Bank Storage • Cell Bank Stability Testing • Raw Material Release Testing • Manufacture of DS • IPC Testing • Release and Stability Testing	Boehringer Ingleheim Pharma GmbH & Co KG, Biberach (BIP) (b) (4) Birkendorfer Strasse 65, 88397 Biberach/Riss Germany	3007748866 ~ 3002806518	PLI Inspection Required	3 Item 483 wsa issued related to: • (b) month storage of DS (b) (4) was not supported • Deviations not adequately investigated and documented • (b) (4) is not adequately maintained	Pre-Approval Inspection Recommendation based on Preapproval inspection review: Approve Facility
Cell Bank Storage	Boehringer Ingelheim RCV GmbH & Co. KG DR.-Boehringer-Gasse 5-11, 1120 Wein, Austria	3003433722	Inspection not required based on GMP risk	N/A	Inspection not required based on GMP risk. 2014 inspection classified VAI.
Stability Testing (b) (4)	(b) (4)		Inspection deferred based on Facility profile	N/A	Facility approved based on profile
IPC Testing (b) (4)			Inspection deferred based on Facility profile	N/A	Facility approved based on profile.
Raw Material Release Testing			Inspection not required based on GMP risk	N/A	An evaluation of this site is not required due to low GMP significance of activities. (b) (4) inspection classified VAI.
DRUG PRODUCT					

• DP manufacturing • DP release testing • DP stability testing • Labeling • Secondary packaging • Identity testing	Boehringer Ingleheim Pharma GmbH & Co KG, Biberach (BIP) (b) (4) Birkendorfer Strasse 65, 88397 Biberach/Riss	3007748866 ~ 3002806518	Inspection deferred based on Facility profile	N/A	DP Facility (b) (4) approved based on profile.
Stability Testing (b) (4	(b) (4)		Inspection deferred based on Facility profile	N/A	Facility approved based on profile
• Labeling • Secondary packaging • Identity testing	Boehringer-Ingelheim Roxane, Inc. 1809 Wilson Road, Columbus, OH 43228	1510690		N/A	Per DIA review, an evaluation of this site is not required due to low GMP significance of activities.

G. Facilities

This BLA proposes manufacture of idarucizumab drug substance and drug product at the following facilities.

Drug Substance:
Boehringer Ingleheim Pharma GmbH & Co (BIP) in Biberach, Germany (FEI #3007748866) is responsible for DS manufacturing, including in-process, release, and stability testing of the DS. Manufacturing has been validated (b) (4) on the BIP Biberach campus.
BIP is also responsible for storage and stability testing of the Master and Working cell banks and for raw material release testing and control.

A pre-license inspection (PLI) for idarucizumab drug substance manufacturing at BIP was conducted from August 3-11 2015 by a team from OPQ/OPF and OPQ/OBP. The inspection focused on drug substance manufacturing. Three 483 observations were made at the conclusion of the inspection of Boehringer Ingelheim Pharma. The inspection was classified as VAI.
Boehringer Ingelheim RCV GmbH & Co. KG in Wien, Austria (FEI 3003433722) is a second cell bank storage site. Although this was assessed as a low risk activity not requiring an evaluation, this site was inspected in 2014 under a surveillance inspection of the DS manufacturer resulting in a VAI classification.

(b) (4) tests DS stability (b) (4) . This facility was approved for this BLA based on its compliance profile following a surveillance and pre-approval inspection of the quality and laboratory systems in (b) (4). The inspection was classified NAI.

[redacted] (b) (4) tests [redacted] (b) (4). This facility was approved based on its compliance profile following a surveillance inspection of the quality, facilities, equipment, laboratory and material systems in [redacted] (b) (4). The inspection was classified NAI.
[redacted] (b) (4) does raw material testing. Although this was assessed as a low risk activity not requiring an evaluation, this site was inspected in [redacted] (b) (4) under a surveillance inspection that covered quality and laboratory systems resulting in a VAI classification.

Drug Product:
The manufacturing of Praxbind vialed drug product, including in-process, release, and stability testing of the DP as well as labeling and secondary packaging is performed at Boehringer Ingleheim Pharma GmbH & Co in Biberach, Germany (FEI #3007748866) in [redacted] (b) (4). This site also performs identity testing per 21 CFR 610.14.

Inspection of the Drug product manufacturing facility was waived for this BLA based on an assessment of the complexity of the manufacturing process, similarity of the process to that of other antibody drug products made at the same facility, and based on the GMP compliance of the facility. This facility status is acceptable based on a routine surveillance GMP inspection conducted in 2014 which covered finished injectable dosage forms including Quality, Materials, Production, Equipment and Facilities, and Packaging and Labeling Systems. An FDA Form 483 was issued. The inspection was classified VAI.

Labeling, secondary packaging and identity testing per 21 CR 610.14 can also be performed at Boehringer-Ingelheim Roxane, Inc., Columbus, OH (FEI 1510690). A GMP surveillance inspection was conducted at this site in August 2015 covering AE and safety reporting. The inspection was classified as VAI.

[redacted] (b) (4) tests DP stability [redacted] (b) (4) [redacted] (b) (4). This facility was approved for this BLA based on its compliance profile following a surveillance and pre-approval inspection of the quality and laboratory systems in [redacted] (b) (4). The inspection was classified NAI.
The facility descriptions submitted in this BLA have been adequately described to support the approval of this submission.

For a complete summary see Appendix E: Drug Substance and Drug Product Facilities Review: Division of Inspectional Assessment.

H. Lifecycle Knowledge Management a. Drug Substance

i. Protocols approved:
   (a) annual DS stability protocol,
   (b) stability protocol for the extension of shelf-life,

(c) reference standard requalification, and qualification of new working
reference standard.
(d) protocols for concurrent validation of [redacted] (b) (4)
(e) protocol for validation of [redacted] (b) (4).
(f) protocol for validation of [redacted] (b) (4)
(g) Cell bank stability protocol

ii. Outstanding review issues/residual risk – none

iii. Future inspection points to consider - none

b. Drug Product

i. Protocols approved:
(a) annual DP stability protocol [redacted] (b) (4)
(b), stability protocol for the extension of shelf-life.
(c) Protocol for [redacted] (b) (4)

ii. Outstanding review issues/residual risk:
none

iii. Future inspection points to consider – none

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist	Yes	No	N/A
	Product Type			
1.	Recombinant Product	X		
2.	Naturally Derived Product		X	
3.	Botanical		X	
4.	Human Cell Substrate/Source Material		X	
5.	Non-Human Primate Cell Substrate/Source Material		X	
6.	Non- Primate Mammalian Cell Substrate/Source Material	X		
7.	Non-Mammalian Cell Substrate/Source Material		X	
8.	Transgenic Animal Sourced		X	
9.	Transgenic Plant Sourced		X	
10.	New Molecular Entity	X		

11.	PEPFAR Drug			X	
12.	PET Drug			X	
13.	Sterile Drug Product		X		
14.	Other_____				
	Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application (#_____)			X	
16.	Comparability Protocol(s)			X	
17.	End of Phase II/Pre-NDA Agreements tem)			X	
18.	SPOTS (Special Products On-line Tracking System			X	
19.	USAN Name Assigned		X		
20.	Other_____				
	Quality Considerations				
21.	Drug Substance Overage			X	
22.	Design Space	Formulation		X	
23.		Process		X	
24.		Analytical Methods		X	
25.		Other			
26.	Other QbD Elements			X	
27.	Real Time Release Testing (RTRT)			X	
28.	Parametric Release in lieu of Sterility Testing			X	
29.	Alternative Microbiological Test Methods			X	
30.	Process Analytical Technology in Commercial Production			X	
31.	Non-compendial Analytical Procedures	Drug Product	X		
32.		Excipients		X	
33.		Drug Substance	X		
34.	Excipients	Human or Animal Origin		X	
35.		Novel		X	
36.	Nanomaterials			X	
37.	Genotoxic Impurities or Structural Alerts			X	
38.	Continuous Manufacturing			X	
39.	Use of Models for Release			X	
40.	Other _____				

Appendices

QUALITY REVIEW STN 761025 Praxbind (idarucizumab)

Appendix A: Drug Substance Quality Review: OBP

BLA STN 761025

PRAXBIND™ (Idarucizumab)

Boehringer Ingelheim Pharmaceuticals, Inc.

DRUG SUBSTANCE REVIEW

Reviewer: Tura Camilli, PhD (Drug Substance) – DBRR I
Reviewer: Lixin Xu. MD, PhD (Characterization, comparability, assay validation) – DBRR IV

Team Leader: Chana Fuchs, PhD –DBRR IV

OFFICE OF BIOTECHNOLOGY PRODUCTS

OBP CMC Review Data Sheet

1. **BLA#:** STN 761025

2. **REVIEW DATE: July 20, 2015**

3. **PRIMARY REVIEW TEAM:**
Medical Officer: Andrew Dmytrijuk
Pharm/Tox: Emily Place
Product Quality Team: Tura C. Camilli, Frederick Mills, Lixin Xu
Microbiology: Maria Candauchacon, Candace Gomez-Broughton
Facilities: Donald Obenhuber
Clinical Pharmacology: Martina Sahre
Statistics: Yuan Li Shen
OBP Labeling: Jibril Abdus-Samad
RPM: Alycia Anderson

4. **MAJOR GRMP DEADLINES**
Filing Meeting: April 20, 2015
Mid-Cycle Meeting: May 15, 2015
Wrap-Up Meeting: September 11, 2015
Primary Review Due: July 20, 2015
Secondary Review Due: July 27, 2015
CDTL Memo Due: September 19, 2015
PDUFA Action Date: October 19, 2015

EDR Location: **\\CDSESUB1\evsprod\BLA761025\761025.enx**

5. **COMMUNICATIONS WITH SPONSOR:**

Communication/Document	Date
CMC Information request#1	04/01/2015
Teleconference	04/22/2015
CMC Information request#2	05/13/2015
CMC Information request#3	05/14/2015
CMC Information request#4	06/16/2015
CMC Information request#5	07/08/2015
CMC Information request#6	07/23/2015
CMC Information request#7	07/28/2015
Teleconference (RS)	07/29/2015
CMC Information request#8	08/03/2015
Teleconference	09/11/2015
CMC Information request#9	09/15/2015
Teleconference	09/18/2015

6. **SUBMISSION(S) REVIEWED:**

Submission	Date Received	Review Completed (Yes/No)
STN 761025/0001	02/19/2015	Yes
STN 761025/0002	04/02/2015	Yes
STN 761025/0003	04/07/2015	Yes
STN 761025/0006	05/13/2015	Yes
STN 761025/0008	05/28/2015	Yes
STN 761025/0007	06/04/2015	Yes
STN 761025/0009	06/26/2015	Yes
STN 761025/0005	07/15/2015	Yes
STN 761025/0012	07/17/2015	Yes
STN 761025/0013	07/17/2015	Yes
STN 761025/0014	08/12/2015	Yes
STN 761025/0018	08/12/2015	Yes
STN 761025/0021	09/22/2015	Yes

7. **DRUG PRODUCT NAME/CODE/TYPE:**
   a. Proprietary Name: PRAXBIND
   b. Trade Name: PRAXBIND
   c. Non-Proprietary/USAN: idarucizumab
   d. Common name: BI 655075
   e. INN Name: idarucizumab
   f. Compendial Name: N/A
   g. OBP systematic name: MABFRAG HUMANIZED (IGG1) ANTI_dabigatran
   h. Other Names: N/A

8. **PHARMACOLOGICAL CATEGORY:** Dabigatran antagonist -Humanized Antibody Fab

9. **DOSAGE FORM:** solution in a single-use vial

10. **STRENGTH/POTENCY:**
    a) The concentration of Idarucizumab drug product is 50 mg/ml
    b) Potency is defined as percent relative to reference standard, using a Fab binding activity assay (SPR) and a thrombin clotting assay.

11. **ROUTE OF ADMINISTRATION:** Intravenous injection

12. **REFERENCED MASTER FILES:** NO DMF FOR DRUG SUBSTANCE

13. **INSPECTIONAL ACTIVITIES:**

A pre-approval inspection (PAI) for idarucizumab drug substance manufacturing at the Boehringer Ingelheim Pharma GmbH & Co KG (BIP), Biberach, Germany facility was conducted

from August 3-11 2015 by OPQ/OPF inspectors Maria Candauchacon, Donald Obenhuber, Wayne Seifert and OPQ/OBP reviewer Lixin Xu. The site is responsible for manufacturing of drug substance and drug product, cell bank storage and stability, and in-process, release and stability testing. The inspection was focus on drug substance manufacturing and testing only. Three 483 observations were made at the conclusion of the inspection of Boehringer Ingelheim Pharma and the inspection was classified as VAI. Drug product inspection was waived based on the assessment by office of compliance.

14. **CONSULTS REQUESTED BY OBP:**
None

15. **QUALITY BY DESIGN ELEMENTS**
Risk assessment and design of experiments based studies were used as part of process development.

16. **PRECEDENTS:** None

17. **ADMINISTRATIVE:**

Tura Camilli, Ph.D., Primary Reviewer, Division of Biotechnology Review and Research I

Tura C. Camilli -S

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Date: 2015.07.21 15:54:59 -04'00'

Lixin Xu, M.D., Ph.D, Primary Reviewer, Division of Biotechnology Review and Research IV

Lixin Xu -S

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Date: 2015.07.21 17:26:57 -04'00'

Chana Fuchs, Ph.D, Team Leader ,Division of Biotechnology Review and Research IV

Chana Fuchs -S

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Date: 2015.07.21 17:19:56 -04'00'

SUMMARY OF DRUG SUBSTANCE MANUFACTURING QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

The Office of Biotechnology Products has reviewed the drug substance section, and has fou nd that the data submitted in this section are adequate to support the conclusion that manufacturing of idarucizumab formulated drug substance is well controlled and leads to a drug substance that is pure and potent. Therefore, approval of BLA 761025 for idarucizumab drug substance is recommended.

II. List Of Deficiencies To Be Communicated
None

III. List Of Post-Marketing Commitments
None

IV. Review Of Common Technical Document-Quality Module 1

A. Environmental Assessment Or Claim Of Categorical Exclusion
A claim for a categorical exclusion is being made under 21 CFR 25.31 (c) for substancesthat occur naturally in the environment. This application is for marketing approval of a biologic product comprised of substances that occur naturally in the environment and approval of this action would not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. To the sponsor's knowledge, no extraordinary circumstances, as described in 21 CFR 25.21, exist that would result in significant impact to the environment from the discharge of this substance.

V. Primary Container Labeling Review
The primary and secondary container labeling review was performed by Jibril Abdus-Samad, OBP, and will be uploaded in a separate document.

VI. Review Of Common Technical Document-Quality Module 3.2
This document contains the review of the information provided on idarucizumab drug substance (Section 3.2.S), adventitious agents safety evaluation (3.2.A), and batch records (3.2.R). The review of module 3.2 is provided below.

APPEARS THIS WAY ON ORIGINAL

DESCRIPTION OF DRUG SUBSTANCE

3.2.S. DRUG SUBSTANCE

3.2.S.1.1 Nomenclature

INN: Idarucizumab
USAN: Not yet available
CAS Registry Number: 1362509-93-0
Company Code Number: BI 655075, 655075-01

3.2.S.1.2 Structure

Idarucizumab is a humanized murine Fab fragment produced in CHO cells that binds to the thrombin inhibitor dabigatran and in doing so, inhibits the anticoagulatory effect of dabigatran. Idarucizumab consists of a light chain (LC, amino acids 1-219) and a heavy chain fragment (HC, amino acids 1-225) covalently linked together by one disulfide bond between cysteine 225 of the heavy chain fragment and cysteine 219 of the light chain. (b) (4) [redacted] (b) (4) [redacted]

Molecular Formula: $C_{2131}H_{3299}N_{555}O_{671}S_{11}$.
Molecular Weight/ Molecular Mass: Based on the amino acid sequence, the molecular mass of Idarucizumab is 47766 Da. (b) (4) [redacted]

3.2.S.1.3 General Properties

See characterization section for properties of idarucizumab in section 3.2.S.3.1.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

The following tables identify manufacturing and operations for idarucizumab:

Table 1: List of manufacturers

Company name	Abbre-viated company	Address	FEI/CFN/DUNS®
Boehringer Ingelheim Pharma GmbH & Co KG, Biberach	BIP	Birkendorfer Strasse 65 88397 Biberach / Riss, Germany	FEI: 3007748866 DUNS: 340700520
Boehringer Ingelheim RCV GmbH & Co. KG	RCV	Dr.-Boehringer-Gasse 5-11 1120 Wien, Austria	FEI: 3003433722 DUNS: 300010883

(b) (4)

[redacted]

Table 2: Manufacturer and operation(s) performed

Table 2 Manufacturer and operation(s) performed

Operation	Manufacturer			
	BIP[1]	RCV[1]	(b) (4)	
Cell bank storage	✓	✓		
Cell bank stability testing	✓			
Manufacture of DS	✓			
IPC testing	✓			
IPC testing (b) (4) (b) (4)				✓
Analytical testing (release)	✓			
Analytical testing (stability)	✓			
Stability testing (b) (4) (b) (4)			✓[2]	

[1] Refer to Table 1 for the full company name and address associated with the abbreviated company name in this table.
[2] Method transfer results are presented in Section 3.2.S.4.3.

Table 10.1 Drug substance alternative assay sites and assays performed

Company name	Current use	Planned use
(b) (4)	Not used (back-up)	(b) (4)
	Not used (back-up)	
	For stability testing : (b) (4)	
	Method transfer results are presented below.	
Company name	**Current use**	**Planned use**

(b) (4)

	Release testing for MCB and WCB: Test for the presence of adventitious viruses in vivo (b) (4)	(b) (4)
	Raw materials testing	(b) (4)

3.2.S.2.2 Description of Manufacturing Process and Process Controls

(b) (4)

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Appendix B: Drug Product Quality Review: OBP

BLA STN 761025

PRAXBIND™ (Idarucizumab)

Boehringer Ingelheim Pharmaceuticals, Inc.

DRUG PRODUCT Review

Reviewer: Frederick Mills, PhD (Drug Product) – DBRR IV

Reviewer: Lixin Xu. MD, PhD (assay validation, Immunogenicity) – DBRR IV

Team Leader: Chana Fuchs, PhD –DBRR IV

OFFICE OF BIOTECHNOLOGY PRODUCTS

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

Idarucizumab solution for injection/infusion 50 mg/mL is a clear to slightly opalescent,

colorless to slightly yellow solution presented as a [redacted] (b) (4) 50 mL

Type 1 glass vials. The formulation is composed of 50 mg/mL idarucizumab, 25 mM sodium acetate/acetate, 220 mM sorbitol and 0.2 g/L (0.02 w%) polysorbate 20 at pH 5.5. The container closure system consists of a Type 1 glass vial, [redacted] (b) (4) stopper and [redacted] (b) (4) overseal with colored button (see Section 3.2.P.7).

Reviewer comments: *The description of the Drug Product is adequate, simply summarizing in brief the chemical content of the DP,* [redacted] (b) (4) *and the container closure, which is reviewed in detail under Pharmaceutical Development and in Section 3.2.P.7. As per 3.2.P.3.3, vials are filled to a target fill volume of* [redacted] (b) (4) *mL. This corresponds to a target fill weight of* [redacted] (b) (4) *g, with a range of* [redacted] (b) (4) *g. This specification was met for* [redacted] (b) (4) *runs during DP process validation, and is consistent with USP<90> for content uniformity.*

3.2.P.2 Pharmaceutical Development

Sponsor provided the following table with their quality target product profile (QTTP) and linkage to the DP critical quality attributes (CQA) for idarucizumab solution for injection/infusion (50 mg/mL)

Quality characteristics	Target for commercial product	Related CQA
Route of administration	Intravenous	None (design aspect)
Pharmaceutical dosage form	Solution	
Posology: Dose regimen	Single dose, 5 g, bolus or [redacted] (b) (4) infusion	
Posology: Dosage strength	50 mL (50 mg/mL)	Identity, Potency, Quantity, Extractable volume
Container closure system	50 mL Type I clear glass vial with coated rubber stopper and [redacted] (b) (4) cap	None (design aspect)
Shelf-life	Claim 30 months	None (design aspect)

Stability	The drug product should be stable for at least 30 months under recommended storage conditions, in-use stability	Particle contamination (visible and subvisible particles), Color, Clarity, Opalescence, Concentration, pH, Osmolality, Purity and Homogeneity.
Appearance	Meets pharmacopoeial requirements for parenteral dosage forms, colorless to slightly yellow, practically free of visible particles and meets pharmacopoeial criteria for	Color, Clarity and degree of opalescence, Visible particles, Subvisible particles
Purity	No product related impurities exceeding the acceptable limits	Purity and heterogeneity
Impurities and Safety	No process related impurities exceeding the acceptable limits	Bacterial endotoxins, Sterility, (b) (4)
Convenience	Rapid administration (i.v. bolus injection or (b) (4) infusion)	None (design aspect)

***Reviewer comments**: Related CQAs for some quality characteristics are identified as "none (design aspects)" by the sponsor while there are related CQAs based on our assessment. For example, related CQAs to the container closure system characteristics (b) (4) The glass vial attributes are specified in 3.2.P.7 as colorless, clear, tubing injection vial, nominal volume 50 mL, (b) (4). Specifications for surface hydrolytic resistance, arsenic, and glass grains are as per USP<660>.*

Table 2 CQA of idarucizumab solution for injection/infusion (50 mg/mL)

CQA	Rationale for choice of CQA
Molecule attributes	
Purity	Impurities must be controlled to levels contributing to the purity target. (b) (4)
Potency	The target potency of the solution must be met in order to ensure that the patient receives the effective dose. Potency must remain in an acceptable range over the
Microbiological attributes & Safety	

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Bacterial endotoxins	The limit for endotoxins of the drug product affects the purity target and is critical to the patient. The harmonized USP/Ph.Eur./JP pharmacopoeial requirements for endotoxins for parenteral preparations must be met.
Sterility	The sterility of the drug product affects the purity target and is critical to the patient. The harmonized USP/Ph.Eur./JP pharmacopoeial requirements for sterility for parenteral preparations must be met.
Pharmaceutical attributes	
Quantity	The drug content of the solution affects the strength target; the solution must be formulated according to the label claim and the drug content must remain in an acceptable range over the shelf life.
Polysorbate 20	(b) (4) (b) (4) and is critical to the patient.
Visible particles	The physical quality of the solution is critical to the patient. Adequate appearance of the parenteral solution ensures safety and efficacy. Pharmacopoeial requirements, essentially free of visible particles, for parenteral preparations must be
Subvisible particles	The physical quality of the solution is critical to the patient. Adequate appearance of the parenteral solution ensures safety and efficacy. The harmonized USP/Ph.Eur. pharmacopoeial requirements for particulate contamination for parenteral preparations must be met.
Clarity and degree of opalescence	The physical quality of the solution is critical to the patient. Adequate appearance of the parenteral solution ensures safety and efficacy. Pharmacopoeial requirements that the solution should be clear or slightly opalescent for parenteral preparations must be met.
Extractable volume	The extractable volume affects the strength target ensuring that the patient receives the labeled amount of drug from each dose. The pharmacopoeial requirements for extractable volume must be met

Appears this way on original

Reviewer comments: *Table 2 above represents a subset of cQAs identified in the DS manufacturing process.* (b) (4)

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

Idarucizumab is a humanized murine Fab fragment directed against the thrombin inhibitor

dabigatran. Idaracizumab (b) (4) drug substance is formulated as an isotonic aqueous solution in a buffer consisting of 25 mM sodium acetate, 220 mM sorbitol and 0.2 g/L Polysorbate 20 at a pH of 5.5, (b) (4) The (b) (4) drug substance has been shown to be stable for (b) months at the (b) (4) °C, and for (b) (4) months at (b) (4) °C. The specification for endotoxin of ≤ (b) (4) EU/mg was established for idarucizumab (b) (4) drug substance and is also suitable for the drug product to comply with endotoxin limits

according to USP <85> and Ph.Eur. 2.6.14. The specification for bioburden is not more than

(b) (4) CFU/100 mL for the (b) (4) drug substance and is low enough to ensure efficiency of the (b) (4) process to provide a sterile drug product.

-

Reviewer comment: *This section is a summary of the properties of the Drug Substance, which is reviewed in the 3.2.S sections. The (b) (4) ^{0}C shelf life in the current BLA is (b) (4) months, as per Section 3.2.S.7.1*

3.2.P.2.1.2 Excipients

Table 3 List of excipients and their functions in idarucizumab solution

Ingredient	Function
Acetic acid, glacial	(b) (4)
Polysorbate 20	
Sodium acetate trihydrate	
Sorbitol	
Water for injection (WFI)	

Reviewer comment

Table 3 adequately describes all excipients and their functions. The excipients meet compendia standards (see Table 1 of 3.2.P.1).

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

(b) (4)

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Appendix C: Drug substance Microbiology Review: DMA

The following 46 pages of Appendix C consist of two Drug Substance Microbiology Reviews which have been withheld in full from this review. The entire Microbiology Reviews dated 07/19/15 and 08/28/15, can be found in the Microbiology/Virology Review Section of this Approval Package

Appendix D: Drug product Microbiology Review: DMA

The following 28 pages of Appendix D consist of a Drug Product Microbiology Review which has been withheld in full from this review. The entire Microbiology Review dated 08/01/14, can be found in the Microbiology/Virology Review Section of this Approval Package.

Appendix E: Drug substance and Drug Product Facilities Review: DIA

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: October 8, 2015

To: Administrative File, STN 761025/0

From: Don Obenhuber and Wayne Seifert, Reviewers, CDER/OPQ/OPF/DIA

Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA

Subject: New Biologic License Application (BLA)

US License: 2006

Applicant: Boehringer Ingleheim Pharmaceuticals, Inc. (BIP)

Mfg Facility: Drug Substance and Drug Product: Boehringer Ingleheim Pharmaceuticals, Inc., Birkendorfer Strasse, 88397 Biberach/Riss Germany (FEI: 3007748866)

Product: Idarucizumab

Dosage: Injection, Intravenous (Injection/Infuson), 2.5 gm/50 ml (50 mg/ml)

Indication: Reverse of the anticoagulant effects of dabigatran.

Due Date: October 19, 2015

Recommendation: This submission is recommended for approval from a facilities assessment perspective.

SUMMARY

The subject BLA proposes manufacture of Idarucizumab Drug Substance (DS) and Drug Product (DP) at Boehringer-Ingelheim Pharma GmbH & Co., Biberach an der Riss, Germany (BIP, FEI 307748866). BIP will also conduct Master and working cell bank storage, and DS and DP IPC testing. Additional cell banking, testing, and packaging operations will be conducted at BIP, Boehringer-Ingelheim RCV GmbH & Co. KG (3003433722), (b) (4) and Boehringer Ingelheim Roxane (FEI 1510690).

Idarucizumab is a humanized murine Fab fragment directed against the thrombin inhibitor dabigatran. All listed DS manufacturing; DP manufacturing, testing and packaging facilities are acceptable. The facility descriptions submitted for this BLA have been reviewed and found to be adequate to support the manufacturer of Idarucizumab DS and DP.

ASSESSMENT

DRUG SUBSTANCE AND DRUG PRODUCT

A listing of the manufacturing and testing facilities for Idarucizumab DS and DP are presented below in Table 1. The inspectional histories and status for these sites are presented below the Table. The DS and DP are both manufactured at Boehringer Ingleheim Pharma GmbH & Co. KG, Biberach (BIP). For this reason, the descriptions of the facilities used for DS and DP manufacture are considered together.

Table 1: Idarucizumab DS and DP Manufacturing and Testing Sites

Site Name	Address	FEI #	Responsibility
Boehringer Ingleheim Pharma GmbH & Co KG, Biberach (BIP)	Birkendorfer Strasse 65 88397 Biberach/Riss Germany	3007748866 ~ 3002806518	Cell Bank Storage Cell Bank Stability Testing Raw Material Release Testing Manufacture of DS IPC Testing Release and Stability Testing
Boehringer Ingelheim RCV GmbH & Co. KG	DR.-Boehringer-Gasse 5-11 1120 Wein Austria	3003433722	Cell Bank Storage
(b) (4)			IPC Testing

	(b) (4)		
(b) (4)			IPC Testing
			Stability Testing
			IPC Testing
			Raw Material Release Testing
Boehringer-Ingelheim Roxane, Inc.	1809 Wilson Road Columbus, OH 43228	1510690	Secondary packaging

Reviewer Comment 1: *The facilities for manufacture and testing of Idarucizumab DS and DP are adequately described.*

INSPECTION HISTORY

- **Boehringer Ingleheim Pharma, FEI: 3002806518 – DS Facility**
  - Inspection conducted (b) (4) . An FDA Form 483 was issued. The inspection was classified VAI.

- Inspection conducted (b) (4) The inspection was classified NAI.

- Inspection conducted (b) (4) A four-item FDA Form 483 was issued. The inspection was classified VAI.

- **Boehringer Ingelheim RCV, FEI: 3003433722 – Cell Bank Storage**
- Inspection conducted (b) (4) An FDA Form 483 was issued. The inspection was classified VAI.

- Inspection conducted (b) (4) The inspection was classified NAI.

- Inspection Conducted (b) (4) An FDA Form 483 was issued. The inspection was classified VAI.

- (b) (4) **– IPC Testing**
- Inspection conducted (b) (4) The inspection was classified VAI.

- Inspection conducted (b) (4) The inspection was classified VAI.

- Inspection conducted (b) (4) . The inspection was classified NAI.

- (b) (4) **– IPC Testing**
- Inspection conducted (b) (4) . The inspection was classified NAI.

- Inspection conducted (b) (4)

(b) (4) The inspection was classified VAI.

- Inspection conducted (b) (4) The inspection was classified OAI.

- (b) (4) – **Stability Testing**
- Inspection conducted (b) (4) The inspection was classified NAI.

- Inspection conducted (b) (4) The inspection was classified NAI.

- Inspection conducted (b) (4) The inspection (b) (4) was classified NAI.

- (b) (4) – **IPC Testing**
- Inspection conducted (b) (4) The inspection was classified NAI.

- Inspection conducted (b) (4) The inspection was classified VAI.

- Inspection conducted (b) (4) The inspection was classified VAI.

- (b) (4) – **Raw Material Release Testing**
- Inspection conducted (b) (4). The inspection was classified VAI.

- Inspection conducte (b) (4) The inspection was classified NAI for GMP.

- **Boehringer-Ingelheim Roxane, Inc. FEI 1510690—Secondary Packaging**
- Inspection conducted (b) (4) The inspection was classified VAI.

CURRENT COMPLIANCE STATUS FOR PROPOSED MANUFACTURING AND TESTING FACILITIES

Boehringer Ingleheim Pharma, FEI 3002806518 – DS Facility

Last inspection [redacted] (b) (4). Next inspection [redacted] (b) (4).

Pre-Approval Inspection Recommendation based on Preapproval inspection review: Approve Facility.

Boehringer Ingelheim RCV, FEI 3003433722 – Cell Bank Storage

Cell Bank Storage is of low significance from a GMP perspective. Therefore, an evaluation of this site is not required.

[redacted] (b) (4) **– IPC Testing**

Facility approved based on profile, with an inspection re-evaluation date of [redacted] (b) (4).

[redacted] (b) (4) **– IPC Testing**

Facility approved based on profile, with an inspection re-evaluation date of [redacted] (b) (4).

[redacted] (b) (4) **– Stability Testing**

Facility approved based on profile, with an inspection re-evaluation date of [redacted] (b) (4)

[redacted] (b) (4) **– IPC Testing**

Facility approved based on profile, with an inspection re-evaluation date of [redacted] (b) (4)

[redacted] (b) (4) **– Raw Material Release Testing**

Excipient testing is of low significance from a GMP perspective. Therefore an evaluation of this site is not required.

Boehringer-Ingelheim Roxane Inc. FEI: 1510690 – Secondary Packaging.

Secondary Packaging is of low significance from a GMP perspective. Therefore an evaluation of this site is not required.

***Reviewer Comment 2**: The proposed DS and DP manufacturing, testing and packaging sites are recommended for approval based on inspectional history.*

3.2.A.1 FACILITIES AND EQUIPMENT

An assessment of the BIP facility proposed for Idarucizumab DS and DP manufacture is presented below.

- **DS Manufacturing Facilities and Equipment**

(b) (4)

[redacted]

(b) (4)

Reviewer Comment 3: *The equipment and facilities used for Idarcucizumab DS manufacture were adequately described and were verified during inspection.*

- **DP Manufacturing Facilities and Equipment**

(b) (4)

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(b) (4)

[redacted]

CONCLUSION

Adequate descriptions were provided for the facilities and equipment proposed for Idarucizumab DS and DP manufacture at BIP. All proposed manufacturing and testing sites are in a state of compliance. The BLA is recommended for approval from a facilities assessment standpoint.

Donald Obenhuber -A

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Date: 2015.10.08 14:45:47 -04'00'

Donald Obenhuber, Ph.D.
Microbiologist
OPF Division of Inspectional Assessment
Branch 1

Wayne E. Seifert -S

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Date: 2015.10.08 14:39:48 -04'00'

Wayne Seifert
Consumer Safety Officer
OPF Division of Inspectional Assessment
Branch 1

Steven Fong -S

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Date: 2015.10.08 14:12:15 -04'00'

Steven Fong, Ph.D.
Microbiologist and Acting Quality Assessment Lead
OPF Division of Inspectional Assessment
Branch 1

BLA STN 761025

PRAXBIND™ (Idarucizumab)

Boehringer Ingelheim Pharmaceuticals, Inc.

DRUG SUBSTANCE REVIEW

Reviewer: Tura Camilli, PhD (Drug Substance) – DBRR I
Reviewer: Lixin Xu. MD, PhD (Characterization, comparability, assay validation) – DBRR IV

Team Leader: Chana Fuchs, PhD –DBRR IV

OFFICE OF BIOTECHNOLOGY PRODUCTS

OBP CMC Review Data Sheet

1. **BLA#:** STN 761025

2. **REVIEW DATE: July 20, 2015**

3. **PRIMARY REVIEW TEAM:**
Medical Officer: Andrew Dmytrijuk
Pharm/Tox: Emily Place
Product Quality Team: Tura C. Camilli, Frederick Mills, Lixin Xu
Microbiology: Maria Candauchacon, Candace Gomez-Broughton
Facilities: Donald Obenhuber
Clinical Pharmacology: Martina Sahre
Statistics: Yuan Li Shen
OBP Labeling: Jibril Abdus-Samad
RPM: Alycia Anderson

4. **MAJOR GRMP DEADLINES**
Filing Meeting: April 20, 2015
Mid-Cycle Meeting: May 15, 2015
Wrap-Up Meeting: September 11, 2015
Primary Review Due: July 20, 2015
Secondary Review Due: July 27, 2015
CDTL Memo Due: September 19, 2015
PDUFA Action Date: October 19, 2015

EDR Location: **\\CDSESUB1\evsprod\BLA761025\761025.enx**

5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document	Date
Information request#1	04/01/2015
Teleconference	04/22/2015
Information request#2	05/13/2015
Information request#3	05/14/2015
Information request#4	06/16/2015
Information request#5	07/08/2015

6. **SUBMISSION(S) REVIEWED:**

Submission	Date Received	Review Completed (Yes/No)
STN 761025/0001	02/19/2015	yes
STN 761025/0002	04/02/2015	yes
STN 761025/0003	04/07/2015	yes
STN 761025/0006	05/13/2015	yes

STN 761025/0008	05/28/2015	yes
STN 761025/0007	06/04/2015	yes
STN 761025/0009	06/26/2015	yes
STN 761025/0005	07/15/2015	yes
STN 761025/0012	07/17/2015	yes

7. **DRUG PRODUCT NAME/CODE/TYPE:**
   a. Proprietary Name: PRAXBIND
   b. Trade Name: PRAXBIND
   c. Non-Proprietary/USAN: idarucizumab
   d. Common name: BI 655075
   e. INN Name: idarucizumab
   f. Compendial Name: N/A
   g. OBP systematic name: MABFRAG HUMANIZED (IGG1) ANTI_dabigatran
   h. Other Names: N/A

8. **PHARMACOLOGICAL CATEGORY:** Dabigatran antagonist -Humanized Antibody Fab

9. **DOSAGE FORM:** solution in a single-use vial

10. **STRENGTH/POTENCY:**
    a) The concentration of Idarucizumab drug product is 50 mg/ml
    b) Potency is defined as percent relative to reference standard, using a Fab binding activity assay (SPR) and a thrombin clotting assay.

11. **ROUTE OF ADMINISTRATION:** Intravenous injection

12. **REFERENCED MASTER FILES:** NO DMF FOR DRUG SUBSTANCE

13. **INSPECTIONAL ACTIVITIES:**

A pre-approval inspection (PAI) for idarucizumab drug substance manufacturing at the Biberach (BIP) facility will be conducted from August 3-11 2015 by OPQ inspectors Maria Caudauchacon, Don Obenhuber and OBP reviewer Lixin Xu. The site is responsible for manufacturing of drug substance, cell bank storage and stability, and in-process, release and stability testing.

14. **CONSULTS REQUESTED BY OBP:**
    None

15. **QUALITY BY DESIGN ELEMENTS**
    Risk assessment and design of experiments based studies were used as part of process development.

16. **PRECEDENTS:** None

17. **ADMINISTRATIVE:**

Tura Camilli, Ph.D., Primary Reviewer, Division of Biotechnology Review and Research I

Tura C. Camilli -S

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Lixin Xu, M.D., Ph.D, Primary Reviewer, Division of Biotechnology Review and Research IV

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