CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208171Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 208171
Review #1

Drug Name/Dosage Form	Monoferric (ferric derisomaltose) injection
Strength	100 mg/mL
Route of Administration	IV
Rx/OTC Dispensed	R_x
Applicant	Pharmacosmos A/S
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	21-Mar-19	All
Amendment	09-May-19	DS
Amendment	10-May-19	DS, Process, Micro
Amendment	10-Jul-19	DS
Amendment	19-Jul-19	DS
Amendment	26-Apr-19	DP
Amendment	06-Aug-19	DP, Micro
Amendment	03-Sept-19	DP
Amendment	19-Sept-19	DP

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Ben Zhang	Rajan Pragani
Drug Product	Rajiv Agarwal	Anamitro Banerjee
Process and Facility	Sridar Thumma	Rakhi Shah
Microbiology	Dionne Coker-Robinson	Neal Sweeney
Biopharmaceutics	n/a	n/a
Regulatory Business Process Manager	Rabiya Hadier	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)	n/a	n/a
Environmental	James Laurenson	n/a

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	Pharmacosmos A/S	(b) (4)	n/a	No Review	Adequate information provided in the NDA
	Type II	Pharmacosmos A/S		n/a	No Review	Adequate information provided in the NDA
(b) (4)	Type III	(b) (4)	(b) (4)	n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type V			n/a	No Review	Adequate information provided in the NDA

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	107331	Iron isomaltoside 1000

2. CONSULTS

N/A

Executive Summary

1. Recommendations and Conclusion on Approvability

OPQ recommends APPROVAL of the NDA 208171 for Monoferric® (Iron isomaltoside 1000) Injection 100 mg/mL. As part of this action, OPQ grants a (b) (4) -month re-test period for the drug substance when stored at room temperature and a 36-month expiration period for the drug product when stored at 20-25°C (68-77°F), with excursions permitted between 15°C to 30°C (59°F to 86°F). There are no outstanding issues and no post-approval quality agreements to be conveyed to the applicant.

2. Summary of Quality Assessments

1. Product Overview

NDA 208171 was submitted for Monoferric® (Iron isomaltoside 1000) Injection 100 mg/mL in accordance with section 505(b)(1) of the Food, Drug and Cosmetic Act. Iron isomaltoside is a parenteral iron compound designed to provide high dosing flexibility. The drug product, Monoferric® (Iron isomaltoside 1000) Injection 100 mg/mL, is indicated for the treatment of iron deficiency anemia (IDA) in adult patients who have intolerance to oral iron, or have had unsatisfactory response to oral iron, (b) (4) and for adult patients who have non-hemodialysis dependent chronic kidney disease (NDD-CKD). Iron isomaltoside 1000 was originally investigated under IND 107331. Isomaltoside 1000 injection is currently approved and marketed in over (b) (4) countries outside of the US under the tradename Monofer®

Iron isomaltoside 1000 is a complex of ferric hydroxide and isomaltoside 1000, an oligosaccharide that has a mean molecular weight of 1000 Daltons. The iron isomaltoside powder is manufactured by Pharmacosmos A/S of Denmark. The drug product, Monoferric® (Iron isomaltoside 1000) Injection 100 mg/mL, is supplied as a sterile, dark brown, opaque aqueous solution containing iron(III) isomaltoside 1000 and WFI. The product will be presented in 1, 5 and 10 mL single-dose vial. The drug product formulation is compatible with plasma and will ensure distribution and uptake in the reticuloendothelial system (RES).

The recommended dosing regimen for Iron Isomaltoside 1000 for injection, 100 mg/mL for patients weighing 50 kg or more is 1000 mg of iron in one dose. The recommended dosing regimen for Iron Isomaltoside 1000 for injection, 100 mg/mL for patients weighing less than 50 kg is 20 mg/kg body weight in one dose. Monoferric treatment may be repeated if iron deficiency anemia reoccurs.

Based on the information provided in this application (original submission and in responses to information requests), OPQ considers all review issues adequately addressed and potential risks to patient safety, product efficacy, and product quality mitigated appropriately. Accordingly, OPQ recommends APPROVAL of NDA 208171 and grants

a (b) (4) month re-test period for the drug substance and a 36-month expiration period for the drug product when stored under controlled room temperature.

Proposed Indication(s) including Intended Patient Population	Indicated for the treatment of iron deficiency anemia (IDA) in adult patients; 1. who have intolerance to oral iron or have had unsatisfactory response to oral iron (b) (4) 2. who have non-hemodialysis dependent chronic kidney disease (NDD-CKD
Duration of Treatment	As needed to treat iron deficiency anemia
Maximum Daily Dose	For patients weighing 50 kg (110 lb) or more: Give Monoferric in one dose as 1000 mg of iron per course. For patients weighing less than 50 kg (110 lb): Give Monoferric in one dose as 20 mg/kg body weight per course.
Alternative Methods of Administration	None

2. Quality Assessment Overview

Drug Substance

The drug substance, ferric derisomaltose (also referred to as Iron isomaltoside 1000) was originally investigated under IND 107331. Isomaltoside 1000 which is a complex of ferric hydroxide and isomaltoside 1000, an oligosaccharide that has a mean molecular weight of 1000 Daltons. Isomaltoside 1000 consists of predominantly (b) (4) Iron Isomaltoside is a dark (b) (4) -brown powder containing (b) (4) iron(III). (b) (4)

The drug substance is manufactured by Pharmacosmos A/S of Denmark. The manufacturing process for isomaltoside 1000 consist of (b) (4) The in-process controls and CQAs for the manufacture of iron isomaltoside powder are clearly defined. The drug substance manufacture for the commercial product is identical to the drug substance used in the pivotal clinical trials. Control of the manufacturing process is critical for the quality of the (b) (4) particles.

The drug substance was characterized by multiple analytical methods (see drug substance chapter for details). A summary of the drug substance characterization and structure elucidation including organic and elemental impurities can be found in the drug substance review.

The drug substance will be packaged in (b) (4) that are placed in an (b) (4) that is placed into a (b) (4) for physical protection. The applicant includes specifications for the individual packaging components and confirms that the (b) (4) comply with 21 CFR 177.1520(c).

Specifications and acceptance criteria for the drug substance are consistent with ICH Q6A and were deemed adequate to ensure the quality of the drug substance as it relates to the safety and efficacy of the drug product. All analytical methods are described in adequate detail and are appropriate for their intended use. All validation parameters (system suitability and system precision, specificity, linearity, range, precision, accuracy, ruggedness, robustness, and stability of solutions) are provided in the NDA.

The applicant included 60 month of long term stability data for the 3 primary batches. The batches were manufactured at the commercial site according to the commercial process and packaged in (b) (4) as described above.

The stability data for the registration batches demonstrated a decreasing trend in the pH however all results were within the proposed acceptance criteria. There were no other notable changes after up to 60 months under long term storage condition. The applicant requested (b) (4) month retest for drug substance when stored under long term conditions (25°C 60%RH). Based on the long term and accelerated stability data, forced degradation studies and stress testing data for the drug substance submitted in this application, the proposed retest period of (b) (4) months for the drug substance when stored at 25°C 60%RH is acceptable and may be granted.

NDA 208171 is recommended for approval from a drug substance perspective.

Drug Product and Drug Process

Monoferric® is a sterile (b) (4) solution containing a complex of iron with isomaltosides of an average molecular weight of 1000 Daltons. The drug product is supplied sterile, dark brown, opaque aqueous solution containing iron(III) isomaltoside 1000 filled. The product will be presented in 1, 5 and 10 mL presentations. The target fill volumes for the 1, 5 and 10 mL vials are (b) (4) spectively.

The drug product, Iron Isomaltoside 1000 for injection, 100 mg/mL, has been manufactured since 2006 and marketed in the European Union since 2010 under the tradename Monofer®. The applicant indicates that iron(III) carbohydrate complex was selected for the following reasons:

(b) (4)

(b) (4)

The recommended dosing regimen for Iron Isomaltoside 1000 for injection, 100 mg/mL for patients weighing 50 kg or more is 1000 mg of iron in one dose. The recommended dosing regimen for Iron Isomaltoside 1000 for injection, 100 mg/mL for patients weighing less than 50 kg is 20 mg/kg body weight in one dose. Monoferric treatment may be repeated if iron deficiency anemia reoccurs.

The drug product formulation includes (b) (4)

The container closure system for the drug product consists (b) (4) and is therefore not considered a primary packaging component.

The proposed process parameters and in-process controls were described in sufficient detail and justified. The applicant demonstrated the suitability of the manufacturing process for the drug product at commercial scale. The description of the manufacturing process includes appropriate in-process controls and operating parameters.

The drug product specifications include appearance, assay, pH, (b) (4) , and molecular weight. The drug product specifications are consistent with ICH Q6A, and are based on batch analyses and stability data. The drug product specifications are adequate to establish the drug product identity, potency and purity and provide adequate controls to ensure the quality of the drug product through the product expiry.

In support of the proposed 36 month expiry, the applicant provided 36 months of primary stability data three commercial batches of each vial presentation manufactured at the (b) (4) site and 12 months of stability data for three commercial scale batches manufactured at the (b) (4) site. All batches were packaged in the aforementioned container closure system and stored (b) (4)

The applicant requested a 36-month expiry for the drug product when stored under controlled room temperature 20 to 25°C (68° to 77°F); excursions permitted to 15 to 30°C (59° to 86°F). The stability data shows consistency over time and supports the proposed expiry. Therefore, based on the available stability data provided, Pharmacosmos A/S proposed and the FDA accepts the expiration dating period of **36 months** for the drug product when stored at stored under controlled room temperature.

The drug product reviewer noted the following Lifecycle Management Considerations:

1. The pH of 5.0-7.0 appears (b) (4)
2. (b) (4)

NDA 208171 is recommended for approval from a drug product and drug product process perspective with an assigned expiry of 36-months.

Quality Microbiology

The drug product is (b) (4) Accordingly, this application is recommended for approval from a quality microbiology perspective.

Facilities:

NDA 208171 included (b) (4) sites and all sites were listed as ready for inspection:

- **Pharmacosmos A/S** – Manufacturer, (b) (4)
- (b) (4)

All facilities listed in NDA 208171 were deemed acceptable for the responsibilities listed in the application. Accordingly, NDA 208171 is recommended for approval from a compliance perspective.

Environmental Assessment

The applicant provided a claim for categorical exclusion and a statement of no extraordinary circumstances under 21 Code of Federal Regulations (CFR) Sections 25.31(b). The applicant also confirms that to the best of their knowledge, there are no extraordinary circumstances that would warrant the preparation of an EA under 21 CFR 25.21. The categorical exclusion cited is appropriate based on the estimated amount of drug to be produced for direct use. The claim of categorical exclusion is therefore acceptable and granted.

3. Special Product Quality Labeling Recommendations (NDA only)

n/a

4. **Final Risk Assessment (see Attachment)**

Attached.

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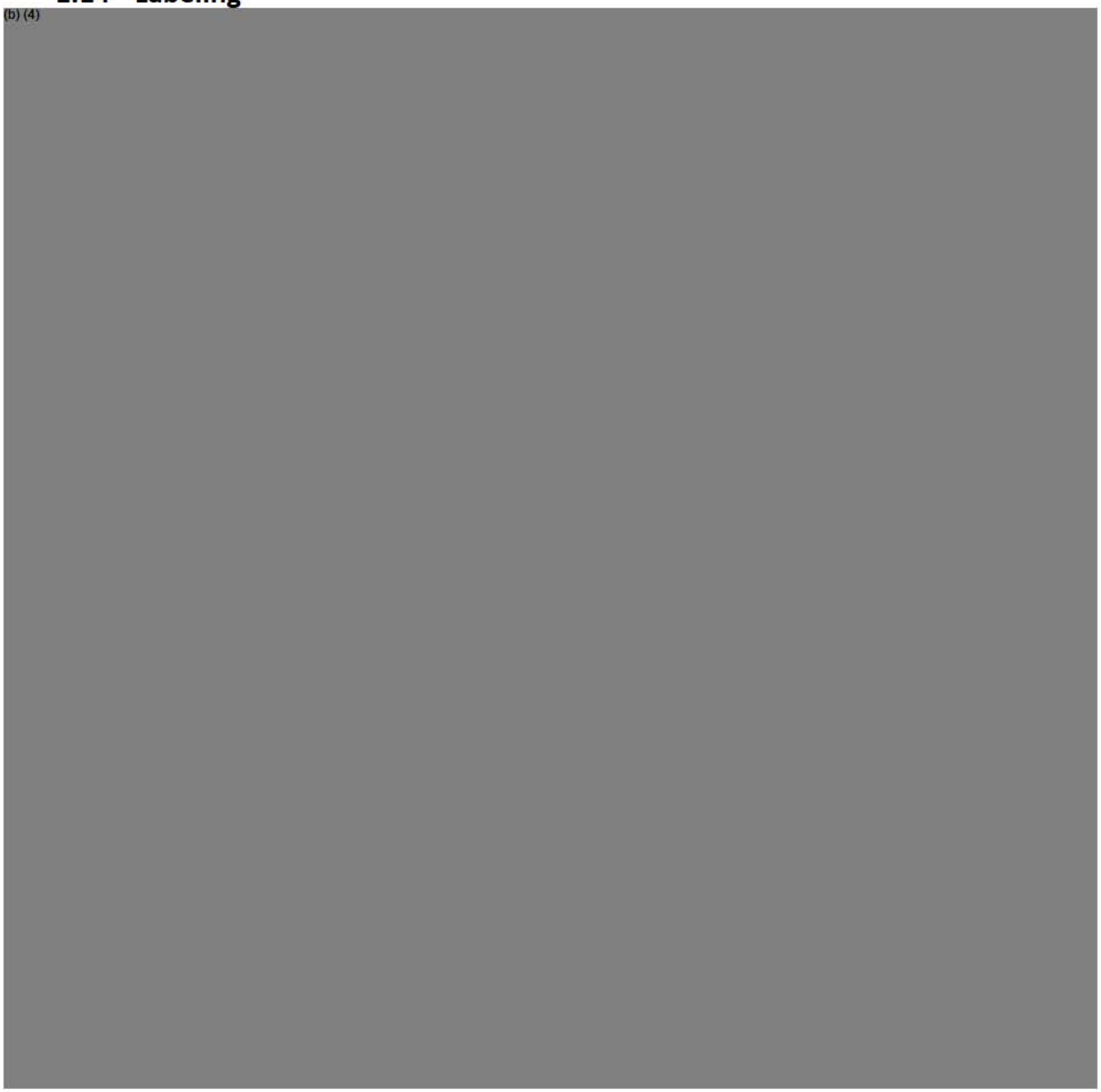
LABELING (NDA 208171)

Review # 1

R Regional Information

1.14 Labeling

(b) (4)



Is the information accurate? ☒ Yes ☐ No
If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

HOW SUPPLIED section:

(b) (4)

[redacted]

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

(b) (4)

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)?

☒ Yes ☐ No ☐ N/A

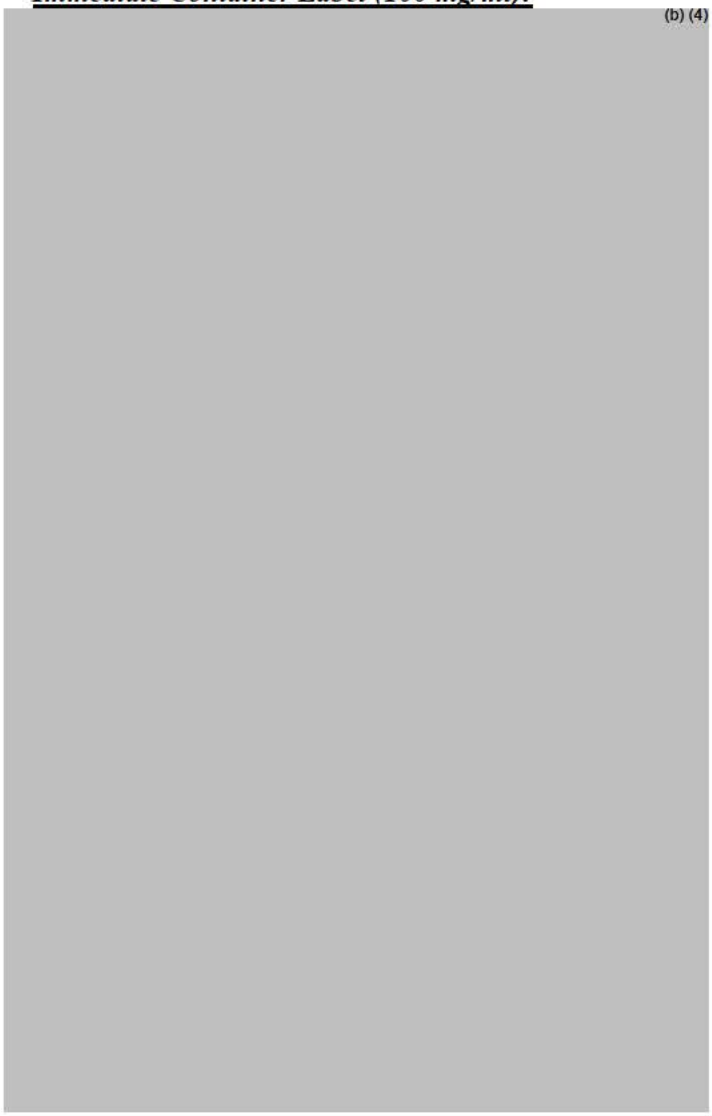
If "No," explain.

Reviewer's Assessment:

The PI label is modified and the comments are communicated to the applicant via OND PM. The applicant has responded satisfarily on 13-DEC-2019. ***Adequate***

Immediate Container Label (100 mg/ml):

(b) (4)



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Carton Label (1000 mg/10 ml):

Reviewer's Assessment: *The comments on labels (primary and secondary) and PI labelling were communicated to the applicant by DMEP/ONDP-DP CMC. The applicant has responsed satisfactorily to the deficiencies on 13-DEC-2019.* ***Adequate***

Conclusion: *Per 21 CFR 201.80 and relevant FDA Labeling Guidances (2018/2019), Labels and Labeling are adequate from a CMC stand point.*

Primary Labeling Reviewer Name and Date:

Rajiv Agarwal, 16-DEC-2019

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Anamitro Banerjee, PhD, December 16, 2019

Rajiv Agarwal

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Anamitro Banerjee

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CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	208171
Assessment Cycle Number	1
Drug Product Name/ Strength	Iron isomaltoside 1000 (Monoferric) / 100 mg/mL (three sizes: 1000 mg/10 mL, 500 mg/5 mL, and 100 mg/1 mL)
Route of Administration	Intravenous injection
Applicant Name	Pharmacosmos A/S
Therapeutic Classification/ OND Division	DHP
Manufacturing Site	Two contract manufacturers: (b) (4)
Method of Sterilization	(b) (4)

Assessment Recommendation: ***Adequate***

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Original Submission (eCTD 0001)	03/21/2019
Response to informational request	05/10/2019
Response to informational request (eCTD 0015)	08/06/2019

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: (b) (4)

(b) (4) The applicant provided adequate validation data. In addition, the applicant was requested to indicate the (b) (4) . The applicant responded that they will perform a microbiological in-use study and provided a draft study protocol similar to USP<51>, but no data was provided. Therefore, a follow up IR was sent on 13 June 2019 requesting a microbiological in-use study and a description of the (b) (4) . The applicant adequately addressed the IR in the response received on 06 August 2019.

Concise Description of Outstanding Issues: None

Supporting Documents:

- (b) (4) (type V) – (b) (4) 14R01.docx dated 11/14/2018. (b) (4) (b) (4) process (adequate).

S DRUG SUBSTANCE

(b) (4) so the drug substance was not reviewed.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –** The drug product is a sterile, dark brown, opaque solution and will be filled into USP Type I glass vials closed with (b) (4) stoppers and (b) (4) caps. Three product presentations will be available: 1000 mg/10 mL, 500 mg/5 mL and 100 mg/1 mL (Section 3.2.P.1 Description and Composition of the Drug Product pg. 1 of 1 and 2.3.P Drug Product pg. 11 of 41).

- **Drug product composition –** The drug product composition is displayed in the applicant supplied table below (Section 3.2.P.1 Description and Composition of the Drug Product, pgs. 1-2 of 2).

Component	Standard	Function	Amount per 1 mL	Percent w/w
Iron isomaltoside 1000	Pharmacosmos A/S	API	(b) (4)	
(b) (4)		(b) (4)		
WFI	Ph. Eur/USP			
(b) (4)		(b) (4)		

- **Description of the container closure system –** The drug product will be supplied in USP type I glass vials, closed with (b) (4) stoppers and sealed with (b) (4) caps. A description of the components that will be used for the container closure system of the three fill volumes is displayed for both manufacturing facilities in the table below. Note that the stoppers used for the 5 mL and 10 mL presentations are identical, and

that the vials and stoppers that will be used for production of the 5 mL and 10 mL presentations are identical between the two manufacturing facilities (Section 3.2.P.7 Container Closure System).

Fill volume	Manufacturing site	Vial	Stopper	Seal
1 mL	(b) (4)			
5 mL				
10 mL				
5 mL				
10 mL				

Adequate

Assessment: The applicant provided an adequate description of the drug product composition and the container closure designed to maintain product sterility.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

Container/Closure and Package Integrity

(b) (4)

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(b) (4)

Adequate

Assessment: The applicant provided an acceptable description of the container closure integrity test, and the container meets regulatory expectations for demonstrating container closure integrity. Data were only provided for the vials used for the 1 mL and 10 mL presentations, not the 5 mL presentation. However, the (b) (4) vial that will be used for the 5 mL presentation is dimensionally equivalent to the (b) (4) vial that will be used for the 10 mL presentation in that the diameter of the vial opening is the same. The vials are also made of the same material, and the stoppers used to close the 5 mL and 10 mL presentations are identical. Therefore, the results of the 10 mL presentation container closure integrity test are applicable to the 5 mL presentation.

Antimicrobial Effectiveness Testing

The drug product is single-use, therefore AET is not required.

Assessment: N/A

P.3 MANUFACTURE

(b) (4)

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John Metcalfe

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Comments: I concur with the primary reviewer's assessment.

Ash Bekele

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ATTACHMENT : Final Risk Assessments

A. Final Risk Assessment – NDA 208171 Monoferric (ferric derimaltose) injection 100 mg/mL

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, stability At release and stability)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	(b) (4)	Acceptable	Controls are in place, continue stability monitoring post approval
Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	Controls are in place,
Uniformity of Dose (Fill Volume/deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipments • Site	L		Acceptable	Controls are in place,
Sterility	• Formulation • Container closure • Process parameters • Scale/equipments • Site	L		Acceptable	Justification is provided, refer to OPF review.
Endotoxin	• Formulation • Container closure • Process parameters • Scale/equipments • Site	L		Acceptable	Justification is provided, refer to OPF review.
pH	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	Controls are in place
Particulate matter (non aggregate for solution only)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	Controls are in place
Leachable extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	USP <381., <660> and <87> tests conform

Rajiv Agarwal

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Anamitro Banerjee

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Sherita McLamore

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