CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 212340

Name: Iron Sucrose; 50MG/2.5 ML, 100MG/5ML, 200MG/10ML

Sponsor: MSN Pharmaceuticals Inc.

Approval Date: August 08, 2025

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 212340

CONTENTS

Reviews / Information Included in this Review

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Chemistry Review(s)	**X**
Bio Pharm/Tox Review	
Bioequivalence Review(s)	**X**
Statistical Review(s)	
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Other Review(s)	**X**
Administrative & Correspondence Documents	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 212340

APPROVAL LETTER

ANDA 212340

ANDA APPROVAL

Sandoz Inc.
100 College Road West
Princeton, NJ 08540
Attention: Gregory Seitz
Head, U.S. Regulatory Affairs Generics

Dear Gregory Seitz:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on August 28, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Iron Sucrose Injection USP, 50 mg Elemental Iron/2.5 mL (20 mg/mL), 100 mg Elemental Iron/5 mL (20 mg/mL), 200 mg Elemental Iron/10 mL (20 mg/mL) (Single-Dose Vials).

Reference is also made to the complete response letter issued by this office on April 17, 2023, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug meets the requirements for approval under the FD&C Act. Accordingly, the ANDA is **approved**, effective on the date of this letter. We have determined your Iron Sucrose Injection USP, 50 mg Elemental Iron/2.5 mL (20 mg/mL), 100 mg Elemental Iron/5 mL (20 mg/mL), 200 mg Elemental Iron/10 mL (20 mg/mL) (Single-Dose Vials) to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Venofer Injection, 50 mg Elemental Iron/2.5 mL (20 mg/mL), 100 mg Elemental Iron/5 mL (20 mg/mL), 200 mg Elemental Iron/10 mL (20 mg/mL), of American Regent, Inc. (American Regent) NDA - 021135.

Please note that if FDA requires a Risk Evaluation and Mitigation Strategy (REMS) for a listed drug, an ANDA referencing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standard for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third

parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website as https://www.uspnf.com/.

REQUIREMENTS AND RECOMMENDATIONS POST APPROVAL

Under applicable statutes, regulations, and guidances, your ANDA may be subject to certain requirements and recommendations post approval, including requirements regarding changes to approved ANDAs, postmarketing reporting, promotional materials, and annual facility fees, among others. For information on post-approval requirements and recommendations for ANDAs and a list of resources for ANDA holders, we refer you to https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/requirements-and-resources-approved-andas.

Sincerely yours,

{See appended electronic signature page}

For Malik Imam, PharmD, MBA
CDR, United States Public Health Service
Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

John Ibrahim

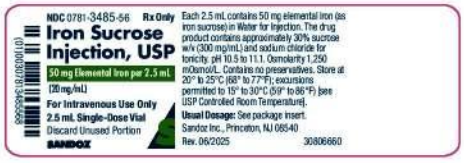
Digitally signed by John Ibrahim
Date: 8/08/2025 10:06:25AM
GUID: 542af06d0124375c12e8c1d9fc86e87c

CENTER FOR DRUG EVALUATION AND RESEARCH

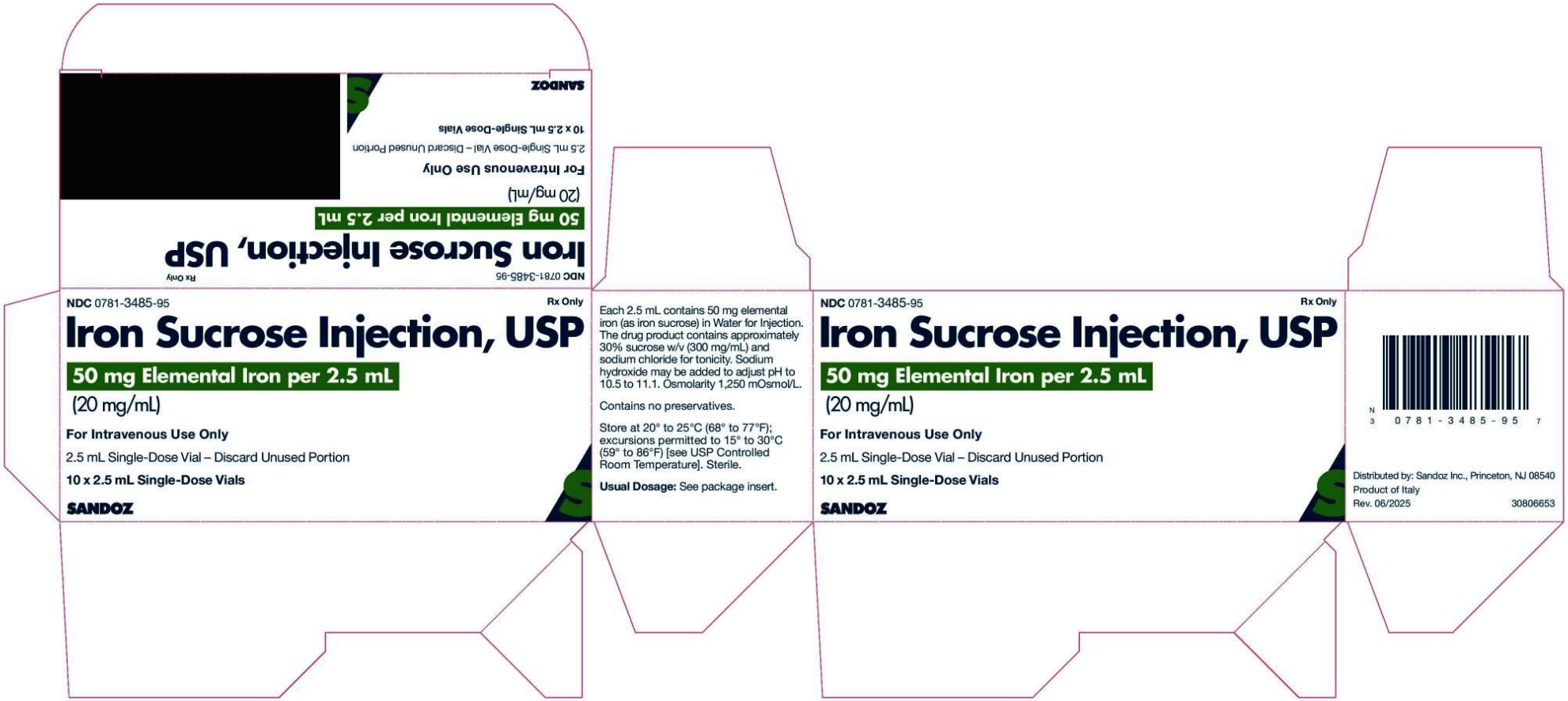
APPLICATION NUMBER:

ANDA 212340

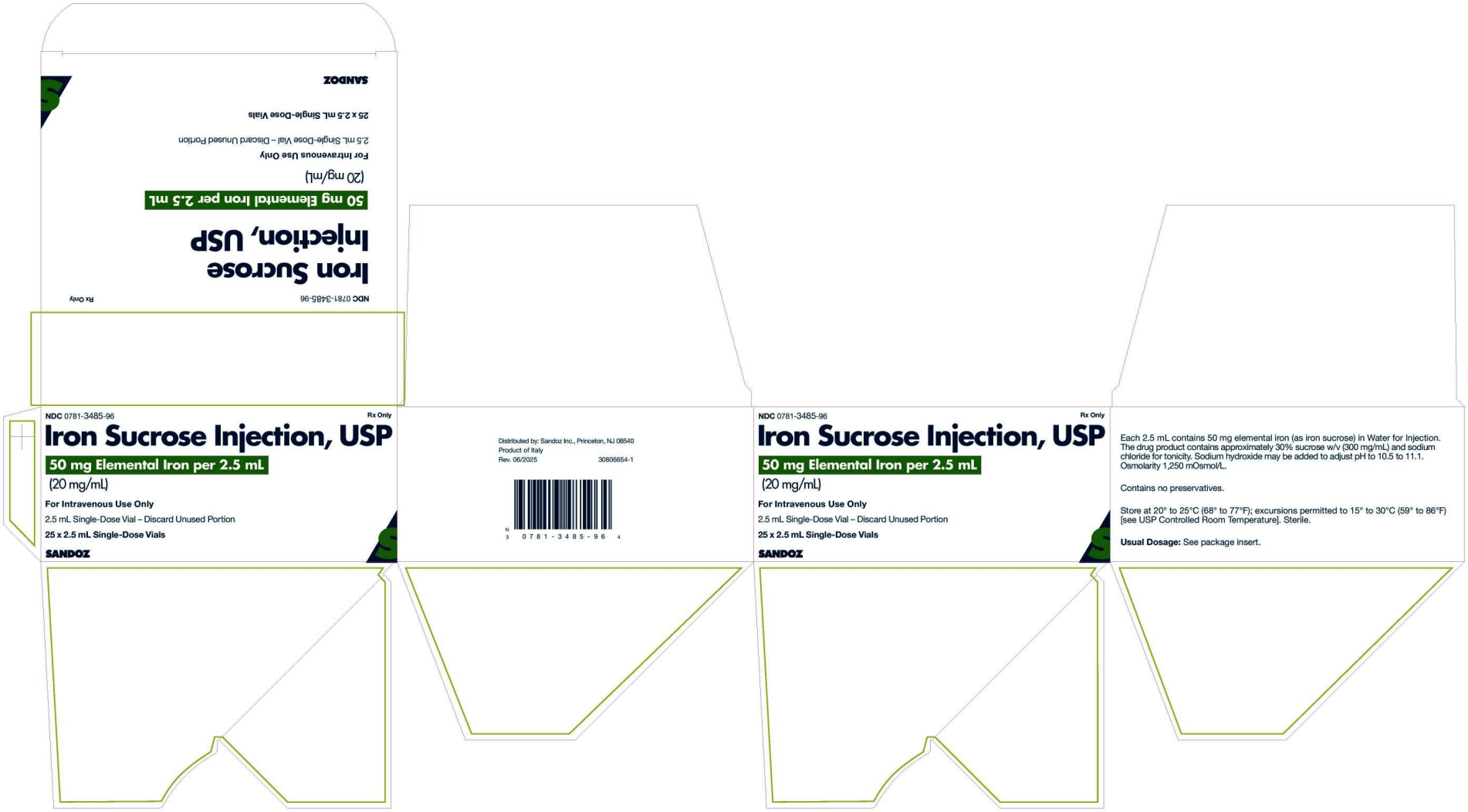
LABELING


NDC 0781-3485-56 Rx Only
Iron Sucrose Injection, USP
50 mg Elemental Iron per 2.5 mL
(20 mg/mL)
For Intravenous Use Only
2.5 mL Single-Dose Vial
Discard Unused Portion
SANDOZ
Each 2.5 mL contains 50 mg elemental iron (as iron sucrose) in Water for Injection. The drug product contains approximately 30% sucrose w/v (300 mg/mL) and sodium chloride for tonicity. pH 10.5 to 11.1. Osmolarity 1,250 mOsmol/L. Contains no preservatives. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].
Usual Dosage: See package insert.
Sandoz Inc., Princeton, NJ 08540
Rev. 06/2025
30806660

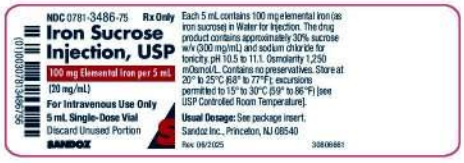
(b)(4)


NDC 0781-3485-95
Rx Only
Iron Sucrose Injection, USP
50 mg Elemental Iron per 2.5 mL
(20 mg/mL)
For Intravenous Use Only
2.5 mL Single-Dose Vial – Discard Unused Portion
10 x 2.5 mL Single-Dose Vials
SANDOZ
Each 2.5 mL contains 50 mg elemental iron (as iron sucrose) in Water for Injection. The drug product contains approximately 30% sucrose w/v (300 mg/mL) and sodium chloride for tonicity. Sodium hydroxide may be added to adjust pH to 10.5 to 11.1. Osmolarity 1,250 mOsmol/L.
Contains no preservatives.
Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Sterile.
Usual Dosage: See package insert.
NDC 0781-3485-95
Rx Only
Iron Sucrose Injection, USP
50 mg Elemental Iron per 2.5 mL
(20 mg/mL)
For Intravenous Use Only
2.5 mL Single-Dose Vial – Discard Unused Portion
10 x 2.5 mL Single-Dose Vials
SANDOZ
N 3 0781-3485-95 7
Distributed by: Sandoz Inc., Princeton, NJ 08540
Product of Italy
Rev. 06/2025
30806653

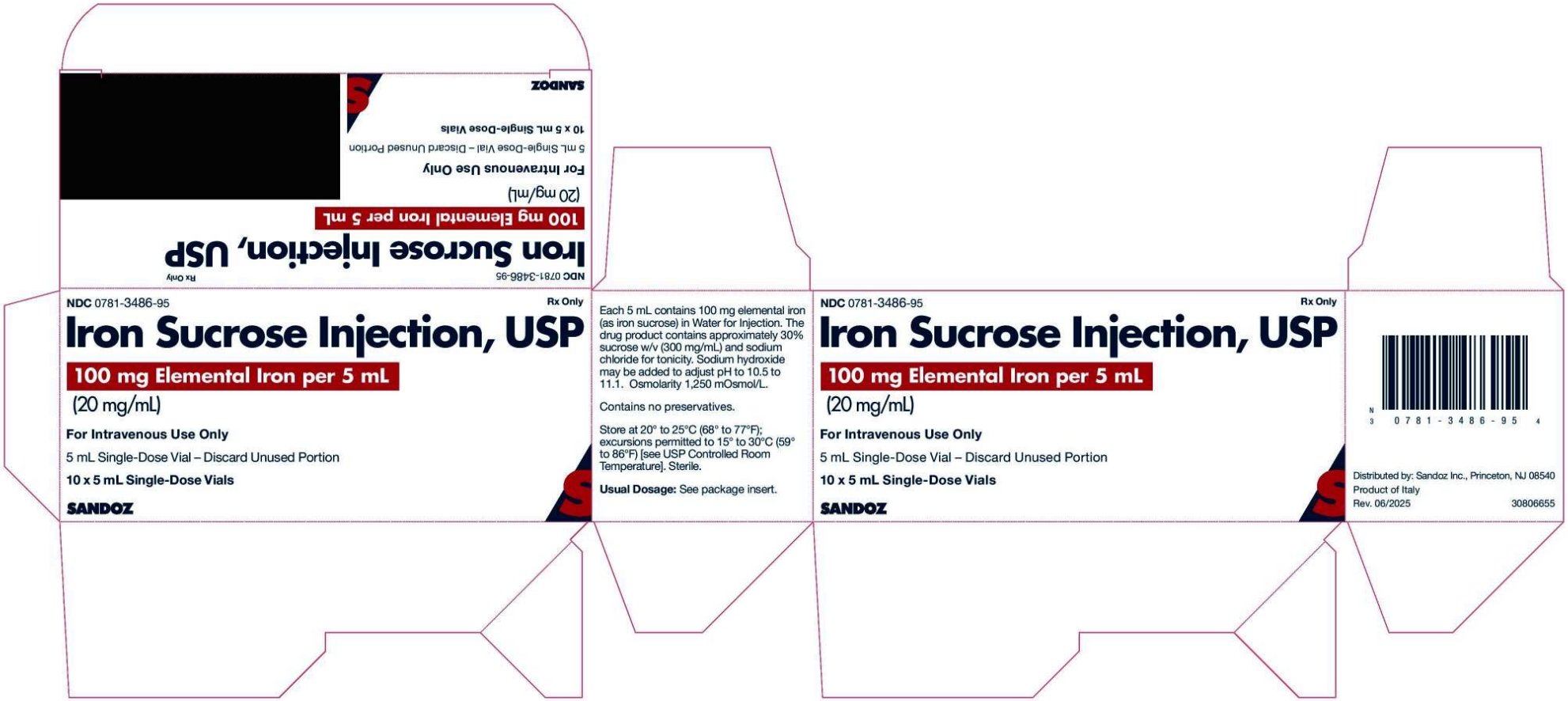
(b)(4)


SANDOZ
25 x 2.5 mL Single-Dose Vials
For Intravenous Use Only
2.5 mL Single-Dose Vial – Discard Unused Portion
(20 mg/mL)
50 mg Elemental Iron per 2.5 mL
Iron Sucrose Injection, USP
NDC 0781-3485-96
Rx Only
NDC 0781-3485-96
Rx Only
Iron Sucrose Injection, USP
50 mg Elemental Iron per 2.5 mL
(20 mg/mL)
For Intravenous Use Only
2.5 mL Single-Dose Vial – Discard Unused Portion
25 x 2.5 mL Single-Dose Vials
SANDOZ
Distributed by: Sandoz Inc., Princeton, NJ 08540
Product of Italy
Rev. 06/2025
30806654-1
N 3 0781-3485-96 4
NDC 0781-3485-96
Rx Only
Iron Sucrose Injection, USP
50 mg Elemental Iron per 2.5 mL
(20 mg/mL)
For Intravenous Use Only
2.5 mL Single-Dose Vial – Discard Unused Portion
25 x 2.5 mL Single-Dose Vials
SANDOZ
Each 2.5 mL contains 50 mg elemental iron (as iron sucrose) in Water for Injection. The drug product contains approximately 30% sucrose w/v (300 mg/mL) and sodium chloride for tonicity. Sodium hydroxide may be added to adjust pH to 10.5 to 11.1. Osmolarity 1,250 mOsmol/L.
Contains no preservatives.
Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Sterile.
Usual Dosage: See package insert.

(b)(4)


NDC 0781-3486-75 Rx Only
Iron Sucrose Injection, USP
100 mg Elemental Iron per 5 mL
(20 mg/mL)
For Intravenous Use Only
5 mL Single-Dose Vial
Discard Unused Portion
SANDOZ
Each 5 mL contains 100 mg elemental iron (as iron sucrose) in Water for Injection. The drug product contains approximately 30% sucrose w/v (300 mg/mL) and sodium chloride for tonicity. pH 10.5 to 11.1. Osmolarity 1,250 mOsmol/L. Contains no preservatives. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].
Usual Dosage: See package insert.
Sandoz Inc., Princeton, NJ 08540
Rev. 09/2025
38806881

(b)(4)


NDC 0781-3486-95
Rx Only
Iron Sucrose Injection, USP
100 mg Elemental Iron per 5 mL
(20 mg/mL)
For Intravenous Use Only
5 mL Single-Dose Vial – Discard Unused Portion
10 x 5 mL Single-Dose Vials
SANDOZ
Each 5 mL contains 100 mg elemental iron (as iron sucrose) in Water for Injection. The drug product contains approximately 30% sucrose w/v (300 mg/mL) and sodium chloride for tonicity. Sodium hydroxide may be added to adjust pH to 10.5 to 11.1. Osmolarity 1,250 mOsmol/L.
Contains no preservatives.
Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Sterile.
Usual Dosage: See package insert.
NDC 0781-3486-95
Rx Only
Iron Sucrose Injection, USP
100 mg Elemental Iron per 5 mL
(20 mg/mL)
For Intravenous Use Only
5 mL Single-Dose Vial – Discard Unused Portion
10 x 5 mL Single-Dose Vials
SANDOZ
N 3 0781-3486-95 4
Distributed by: Sandoz Inc., Princeton, NJ 08540
Product of Italy
Rev. 06/2025
30806655

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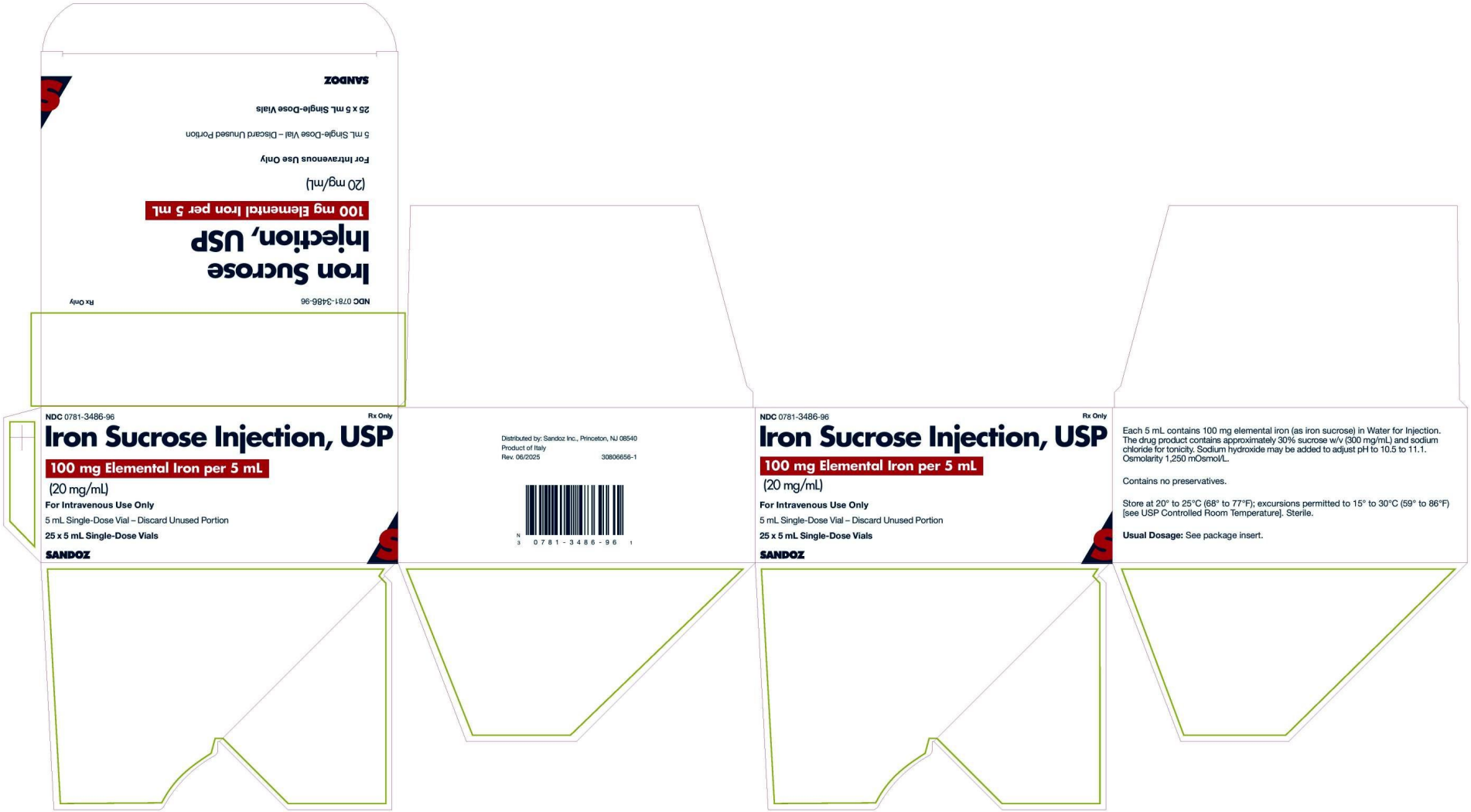
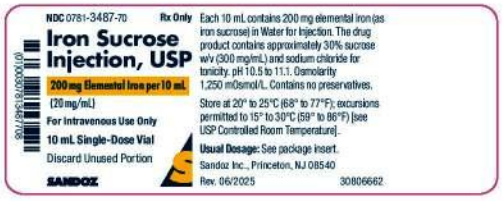

NDC 0781-3486-96
Rx Only
Iron Sucrose Injection, USP
100 mg Elemental Iron per 5 mL
(20 mg/mL)
For Intravenous Use Only
5 mL Single-Dose Vial – Discard Unused Portion
25 x 5 mL Single-Dose Vials
SANDOZ
NDC 0781-3486-96
Rx Only
Iron Sucrose Injection, USP
100 mg Elemental Iron per 5 mL
(20 mg/mL)
For Intravenous Use Only
5 mL Single-Dose Vial – Discard Unused Portion
25 x 5 mL Single-Dose Vials
SANDOZ
Distributed by: Sandoz Inc., Princeton, NJ 08540
Product of Italy
Rev. 06/2025
30806656-1
N 3 0781-3486-96 1
NDC 0781-3486-96
Rx Only
Iron Sucrose Injection, USP
100 mg Elemental Iron per 5 mL
(20 mg/mL)
For Intravenous Use Only
5 mL Single-Dose Vial – Discard Unused Portion
25 x 5 mL Single-Dose Vials
SANDOZ
Each 5 mL contains 100 mg elemental iron (as iron sucrose) in Water for Injection. The drug product contains approximately 30% sucrose w/v (300 mg/mL) and sodium chloride for tonicity. Sodium hydroxide may be added to adjust pH to 10.5 to 11.1. Osmolarity 1,250 mOsmol/L.
Contains no preservatives.
Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Sterile.
Usual Dosage: See package insert.

(b)(4)


NDC 0781-3487-70
Rx Only
Iron Sucrose Injection, USP
200 mg Elemental Iron per 10 mL
(20 mg/mL)
For Intravenous Use Only
10 mL Single-Dose Vial
Discard Unused Portion
SANDOZ
Each 10 mL contains 200 mg elemental iron (as iron sucrose) in Water for Injection. The drug product contains approximately 30% sucrose w/v (300 mg/mL) and sodium chloride for tonicity. pH 10.5 to 11.1. Osmolarity 1,250 mOsmol/L. Contains no preservatives.
Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].
Usual Dosage: See package insert.
Sandoz Inc., Princeton, NJ 08540
Rev. 06/2025
30806662

(b)(4)


NDC 0781-3487-14
Rx Only
Iron Sucrose Injection, USP
200 mg Elemental Iron per 10 mL
(20 mg/mL)
Each 10 mL contains 200 mg elemental iron (as iron sucrose) in Water for Injection. The drug product contains approximately 30% sucrose w/v (300 mg/mL) and sodium chloride for tonicity. Sodium hydroxide may be added to adjust pH to 10.5 to 11.1. Osmolarity 1,250 mOsmol/L.
Contains no preservatives.
Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Sterile.
Usual Dosage: See package insert.
N 3 0781-3487-14 2
NDC 0781-3487-14
Rx Only
Iron Sucrose Injection, USP
200 mg Elemental Iron per 10 mL
(20 mg/mL)
For Intravenous Use Only
10 mL Single-Dose Vial – Discard Unused Portion
5 x 10 mL Single-Dose Vials
SANDOZ
Distributed by:
Sandoz Inc.,
Princeton, NJ 08540
Product of Italy
Rev. 06/2025 30806658

(b)(4)


NDC 0781-3487-92
Rx Only
Iron Sucrose Injection, USP
200 mg Elemental Iron per 10 mL
(20 mg/mL)
Each 10 mL contains 200 mg elemental iron (as iron sucrose) in Water for Injection. The drug product contains approximately 30% sucrose w/v (300 mg/mL) and sodium chloride for tonicity. Sodium hydroxide may be added to adjust pH to 10.5 to 11.1. Osmolarity 1,250 mOsmol/L.
Contains no preservatives.
Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Sterile.
Usual Dosage: See package insert.
N 3 0781-3487-92 0
NDC 0781-3487-92
Rx Only
Iron Sucrose Injection, USP
200 mg Elemental Iron per 10 mL
(20 mg/mL)
For Intravenous Use Only
10 mL Single-Dose Vial – Discard Unused Portion
10 x 10 mL Single-Dose Vials
SANDOZ
Distributed by:
Sandoz Inc.,
Princeton, NJ 08540
Product of Italy
Rev. 06/2025
XXXXXXX

(b)(4)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use IRON SUCROSE INJECTION safely and effectively. See full prescribing information for IRON SUCROSE Injection.

IRON SUCROSE injection, for intravenous use
Initial U.S. Approval: 2000

INDICATIONS AND USAGE

Iron sucrose injection is an iron replacement product indicated for the treatment of iron deficiency anemia (IDA) in patients with chronic kidney disease (CKD). (1)

DOSAGE AND ADMINISTRATION

Population		Dose
Adult patients	Hemodialysis Dependent-Chronic Kidney Disease (HDD-CKD) (2.2)	100 mg slow intravenous injection or infusion
	Non-Dialysis Dependent-Chronic Kidney Disease (NDD-CKD) (2.3)	200 mg slow intravenous injection or infusion
	Peritoneal Dialysis Dependent-Chronic Kidney Disease (PDD-CKD) (2.4)	300 mg or 400 mg intravenous infusion
Pediatric patients	HDD-CKD (2.5), PDD-CKD or NDD-CKD (2.6)	0.5 mg/kg slow intravenous injection or infusion

DOSAGE FORMS AND STRENGTHS

Injection: 50 mg/2.5 mL, 100 mg/5 mL, or 200 mg/10 mL (20 mg/mL) in single-dose vials. (3)

CONTRAINDICATIONS

- Known hypersensitivity to iron sucrose. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions: Observe for signs and symptoms of hypersensitivity during and after iron sucrose administration for at least 30 minutes and until clinically stable following completion of each administration. Only administer iron sucrose when personnel and therapies are immediately available for the treatment of serious hypersensitivity reactions. (5.1)
- Hypotension: May cause hypotension. Monitor for signs and symptoms of hypotension during and following each administration. (5.2)
- Iron Overload: Regularly monitor hematologic responses during therapy. Do not administer to patients with iron overload. (5.3)

ADVERSE REACTIONS

- Adult patients: The most common adverse reactions (≥2%) are diarrhea, nausea, vomiting, headache, dizziness, hypotension, pruritus, pain in extremity, arthralgia, back pain, muscle cramp, injection site reactions, chest pain and peripheral edema. (6.1)
- Pediatric patients: The most common adverse reactions (≥2%) are headache, respiratory tract viral infection, peritonitis, vomiting, pyrexia, dizziness, cough, nausea, arteriovenous fistula thrombosis, hypotension and hypertension. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 06/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Iron sucrose injection is indicated for the treatment of iron deficiency anemia (IDA) in patients with chronic kidney disease (CKD).

2 DOSAGE AND ADMINISTRATION

2.1 Mode of Administration

Administer iron sucrose injection only intravenously by slow injection or by infusion. The dosage of iron sucrose injection is expressed in mg of elemental iron. Each mL contains 20 mg of elemental iron.

2.2 Adult Patients with Hemodialysis Dependent-Chronic Kidney Disease (HDD-CKD)

Administer iron sucrose injection 100 mg undiluted as a slow intravenous injection over 2 to 5 minutes, or as an infusion of 100 mg diluted in a maximum of 100 mL of 0.9% NaCl over a period of at least 15 minutes, per consecutive hemodialysis session *[see How Supplied/Storage and Handling (16.2)]*. Administer iron sucrose injection early during the dialysis session (generally within the first hour). The usual total treatment course of iron sucrose injection is 1000 mg. Iron sucrose injection treatment may be repeated if iron deficiency reoccurs.

2.3 Adult Patients with Non-Dialysis Dependent-Chronic Kidney Disease (NDD-CKD)

Administer iron sucrose injection 200 mg undiluted as a slow intravenous injection over 2 to 5 minutes or as an infusion of 200 mg in a maximum of 100 mL of 0.9% NaCl over a period of 15 minutes. Administer on 5 different occasions over a 14 day period. There is limited experience with administration of an infusion of 500 mg of iron sucrose injection, diluted in a maximum of 250 mL of 0.9% NaCl, over a period of 3.5 to 4 hours on Day 1 and Day 14 *[see How Supplied/Storage and Handling (16.2).]* Iron sucrose injection treatment may be repeated if iron deficiency reoccurs.

2.4 Adult Patients with Peritoneal Dialysis Dependent-Chronic Kidney Disease (PDD-CKD)

Administer iron sucrose injection in 3 divided doses, given by slow intravenous infusion, within a 28 day period: 2 infusions each of 300 mg over 1.5 hours 14 days apart followed by one 400 mg infusion over 2.5 hours 14 days later. Dilute iron sucrose injection in a maximum of 250 mL of 0.9% NaCl *[see How Supplied/Storage and Handling (16.2)]*. Iron sucrose injection treatment may be repeated if iron deficiency reoccurs.

2.5 Pediatric Patients (2 Years of Age and Older) with HDD-CKD for Iron Maintenance Treatment

For iron maintenance treatment: Administer iron sucrose injection at a dose of 0.5 mg/kg, not to exceed 100 mg per dose, every two weeks for 12 weeks given undiluted by slow intravenous injection over 5 minutes or diluted in 0.9% NaCl at a concentration of 1 to 2 mg/mL and administered over 5 to 60 minutes. Do not dilute to concentrations below 1 mg/mL *[see How Supplied/Storage and Handling [16.2])*. Iron sucrose injection treatment may be repeated if necessary.

The dosing for iron replacement treatment in pediatric patients with HDD-CKD has not been established.

2.6 Pediatric Patients (2 Years of Age and Older) with NDD-CKD or PDD-CKD who are on Erythropoietin Therapy for Iron Maintenance Treatment

For iron maintenance treatment: Administer iron sucrose injection at a dose of 0.5 mg/kg, not to exceed 100 mg per dose, every four weeks for 12 weeks given undiluted by slow intravenous injection over 5 minutes or diluted in 0.9% NaCl at a concentration of 1 to 2 mg/mL and administered over 5 to 60 minutes. Do not dilute to concentrations below 1 mg/mL *[see How Supplied/Storage and Handling (16.2).]* Iron sucrose injection treatment may be repeated if necessary.

The dosing for iron replacement treatment in pediatric patients with NDD-CKD or PDD-CKD has not been established.

3 DOSAGE FORMS AND STRENGTHS

Injection: 50 mg/2.5 mL, 100 mg/5 mL, or 200 mg/10 mL (20 mg/mL) in single-dose vials.

4 CONTRAINDICATIONS

- Known hypersensitivity to iron sucrose.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving iron sucrose. Patients may present with shock, clinically significant hypotension, loss of consciousness, and/or collapse. If hypersensitivity reactions or signs of intolerance occur during administration, stop iron sucrose immediately. Monitor patients for signs and symptoms of hypersensitivity during and after iron sucrose administration for at least 30 minutes and until clinically stable following completion of the infusion. Only administer iron sucrose when personnel and therapies are immediately available for the treatment of serious hypersensitivity reactions. Most reactions associated with intravenous iron preparations occur within 30 minutes of the completion of the infusion *[see Adverse Reactions (6.1 and 6.2)]*.

5.2 Hypotension

Iron sucrose may cause clinically significant hypotension. Monitor for signs and symptoms of hypotension following each administration of iron sucrose. Hypotension following administration of iron sucrose may be related to the rate of administration and/or total dose administered *[see Dosage and Administration (2), Warnings and Precautions (5.1), and Adverse Reactions (6.2)]*.

5.3 Iron Overload

Excessive therapy with parenteral iron can lead to excess storage of iron with the possibility of iatrogenic hemosiderosis. All adult and pediatric patients receiving iron sucrose require periodic monitoring of hematologic and iron parameters (hemoglobin, hematocrit, serum ferritin and transferrin saturation). Do not administer iron sucrose to patients with evidence of iron overload. Transferrin saturation (TSAT) values increase rapidly after intravenous administration of iron sucrose; do not perform serum iron measurements for at least 48 hours after intravenous dosing *[see Dosage and Administration (2) and Overdosage (10)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
- Hypotension *[see Warnings and Precautions (5.2)]*
- Iron Overload *[see Warnings and Precautions (5.3)]*

6.1 Adverse Reactions in Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug may not reflect the rates observed in practice.

Adverse Reactions in Adult Patients with CKD

The frequency of adverse reactions associated with the use of iron sucrose has been documented in six clinical trials involving 231 patients with HDD-CKD, 139 patients with NDD-CKD and 75 patients with PDD-CKD. Adverse reactions

reported by ≥2% of treated patients in the six clinical trials for which the rate for iron sucrose exceeds the rate for comparator are listed by indication in **Table 1**. Patients with HDD-CKD received 100 mg doses at 10 consecutive dialysis sessions until a cumulative dose of 1000 mg was administered. Patients with NDD-CKD received either 5 doses of 200 mg over 2 weeks or 2 doses of 500 mg separated by fourteen days, and patients with PDD-CKD received 2 doses of 300 mg followed by a dose of 400 mg over a period of 4 weeks.

Table 1. Adverse Reactions Reported in ≥2% of Study Populations and for which the Rate for Iron Sucrose Exceeds the Rate for Comparator

Body System/Adverse Reactions	HDD-CKD	NDD-CKD		PDD-CKD	
	Iron Sucrose (N=231) %	Iron Sucrose (N=139) %	Oral Iron (N=139) %	Iron Sucrose (N=75) %	EPO* Only (N=46) %
Subjects with any adverse reaction	78.8	76.3	73.4	72.0	65.2
Ear and Labyrinth Disorders					
Ear Pain	0	2.2	0.7	0	0
Eye Disorders					
Conjunctivitis	0.4	0	0	2.7	0
Gastrointestinal Disorders					
Abdominal pain	3.5	1.4	2.9	4.0	6.5
Diarrhea	5.2	7.2	10.1	8.0	4.3
Dysgeusia	0.9	7.9	0	0	0
Nausea	14.7	8.6	12.2	5.3	4.3
Vomiting	9.1	5.0	8.6	8.0	2.2
General Disorders and Administration Site Conditions					
Asthenia	2.2	0.7	2.2	2.7	0
Chest pain	6.1	1.4	0	2.7	0
Feeling abnormal	3.0	0	0	0	0
Infusion site pain or burning	0	5.8	0	0	0
Injection site extravasation	0	2.2	0	0	0
Peripheral edema	2.6	7.2	5.0	5.3	10.9
Pyrexia	3.0	0.7	0.7	1.3	0
Infections and Infestations					
Nasopharyngitis, Sinusitis, Upper respiratory tract infections, Pharyngitis	2.6	2.2	4.3	16.0	4.3
Injury, Poisoning and Procedural Complications					
Graft complication	9.5	1.4	0	0	0
Metabolism and Nutrition Disorders					
Fluid overload	3.0	1.4	0.7	1.3	0
Gout	0	2.9	1.4	0	0
Hyperglycemia	0	2.9	0	0	2.2

Hypoglycemia	0.4	0.7	0.7	4.0	0
Musculoskeletal and Connective Tissue Disorders					
Arthralgia	3.5	1.4	2.2	4.0	4.3
Back pain	2.2	2.2	3.6	1.3	4.3
Muscle cramp	29.4	0.7	0.7	2.7	0
Myalgia	0	3.6	0	1.3	0
Pain in extremity	5.6	4.3	0	2.7	6.5
Nervous System Disorders					
Dizziness	6.5	6.5	1.4	1.3	4.3
Headache	12.6	2.9	0.7	4.0	0
Respiratory, Thoracic and Mediastinal Disorders					
Cough	3.0	2.2	0.7	1.3	0
Dyspnea	3.5	5.8	1.4	1.3	2.2
Nasal congestion	0	1.4	2.2	1.3	0
Skin and Subcutaneous Tissue Disorders					
Pruritus	3.9	2.2	4.3	2.7	0
Vascular Disorders					
Hypertension	6.5	6.5	4.3	8.0	6.5
Hypotension	39.4	2.2	0.7	2.7	2.2

*EPO=Erythropoietin

One hundred thirty (11%) of the 1,151 patients evaluated in the 4 U.S. trials in HDD-CKD patients (studies A, B and the two post marketing studies) had prior other intravenous iron therapy and were reported to be intolerant (defined as precluding further use of that iron product). When these patients were treated with iron sucrose there were no occurrences of adverse reactions that precluded further use of iron sucrose *[see Warning and Precautions (5)]*.

Adverse Reactions in Pediatric Patients with CKD (ages 2 years and older)

In a randomized, open-label, dose-ranging trial for iron maintenance treatment with iron sucrose in pediatric patients with CKD on stable erythropoietin therapy *[see Clinical Studies (14.7)]*, at least one adverse reaction was experienced by 57% (27/47) of the patients receiving iron sucrose 0.5 mg/kg, 53% (25/47) of the patients receiving iron sucrose 1 mg/kg, and 55% (26/47) of the patients receiving iron sucrose 2 mg/kg.

A total of 5 (11%) subjects in the iron sucrose 0.5 mg/kg group, 10 (21%) patients in the iron sucrose 1 mg/kg group, and 10 (21%) patients in the iron sucrose 2 mg/kg group experienced at least 1 serious adverse reaction during the study. The most common adverse reactions (greater than 2% of patients) in all patients were headache (6%), respiratory tract viral infection (4%), peritonitis (4%), vomiting (4%), pyrexia (4%), dizziness (4%), cough (4%), nausea (3%), arteriovenous fistula thrombosis (2%), hypotension (2%), and hypertension (2.1%).

6.2 Adverse Reactions from Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of iron sucrose. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In the post-marketing safety studies in 1,051 treated patients with HDD-CKD, the adverse reactions reported by greater than 1% were cardiac failure congestive, sepsis and dysgeusia.

- *Immune system disorders:* anaphylactic-type reactions, angioedema

- *Psychiatric disorders:* confusion
- *Nervous system disorders:* convulsions, collapse, light-headedness, loss-of-consciousness
- *Cardiovascular System:* bradycardia, shock, acute myocardial ischemia with or without myocardial infarction or with in-stent thrombosis in the context of a hypersensitivity reaction.
- *Respiratory, thoracic and mediastinal disorders:* bronchospasm, dyspnea
- *Musculoskeletal and connective tissue disorders:* back pain, swelling of the joints
- *Renal and urinary disorders:* chromaturia
- *General disorders and administration site conditions:* hyperhidrosis

Symptoms associated with iron sucrose total dosage or infusing too rapidly included hypotension, dyspnea, headache, vomiting, nausea, dizziness, joint aches, paresthesia, abdominal and muscle pain, edema, and cardiovascular collapse. These adverse reactions have occurred up to 30 minutes after the administration of iron sucrose injection. Reactions have occurred following the first dose or subsequent doses of iron sucrose. Symptoms may respond to intravenous fluids, hydrocortisone, and/or antihistamines. Slowing the infusion rate may alleviate symptoms.

Injection site discoloration has been reported following extravasation. Assure stable intravenous access to avoid extravasation.

7 DRUG INTERACTIONS

Iron sucrose may reduce the absorption of concomitantly administered oral iron preparations.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Published studies on intravenous iron sucrose treatment after the first trimester of pregnancy have not shown adverse maternal or fetal outcomes *(see Data)*. Available reports of intravenous iron sucrose use in pregnant women during the first trimester are insufficient to assess the risk of major birth defects and miscarriage. There are risks to the mother and fetus associated with untreated IDA in pregnancy as well as risks to the fetus associated with maternal severe hypersensitivity reactions (*see Clinical Considerations*). Animal reproduction studies of iron sucrose administered to rats and rabbits during the period of organogenesis at elemental iron doses equivalent to the maximum recommended human dose based on body surface area revealed no evidence of harm to the fetus *(see Data)*. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically-recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Iron deficiency anemia during pregnancy should be treated. Untreated IDA in pregnancy is associated with adverse maternal outcomes such as post-partum anemia. Adverse pregnancy outcomes associated with IDA include increased risk for preterm delivery and low birth weight.

Fetal/Neonatal Adverse Reactions

Severe adverse reactions including circulatory failure (severe hypotension, shock including in the context of anaphylactic reaction) may occur in pregnant women with parenteral iron products (such as iron sucrose) which may cause fetal bradycardia, especially during the second and third trimester.

Data

Human Data

Published data from randomized controlled studies and prospective observational studies on the use of iron sucrose in pregnant women have not reported an association of iron sucrose and adverse developmental outcomes. However, these studies did not include women exposed during the first trimester of pregnancy and were not designed to assess the risk of major birth defects. Maternal adverse events reported in these studies are similar to those reported during clinical trials in adult males and non-pregnant females *[see Adverse Reactions (6.1)]*.

Animal Data

Iron sucrose was administered intravenously to rats and rabbits during the period of organogenesis at elemental iron doses up to 13 mg/kg/day (0.25 times or equivalent to the maximum recommended human dose based on body surface area, respectively) and revealed no evidence of harm to the fetus.

8.2 Lactation

Risk Summary

Iron sucrose is present in human milk, and available published reports following exposure to 100 to 300 mg intravenous iron sucrose have not reported adverse reactions in breastfed infants *(see Data)*. There are no data on the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for iron sucrose and any potential adverse effects on the breastfed child from iron sucrose or from the underlying maternal condition.

Data

A published study showed no difference in iron concentration in the colostrum of 10 iron deficient breastfeeding women who were 2 to 3 days postpartum and received a single dose of 100 mg of intravenous iron sucrose compared to 5 breastfeeding women who received no iron. These results may underestimate the amount of iron in breastmilk following the standard dose of iron sucrose.

A published report of 78 breastfeeding women who received 300 mg of intravenous iron sucrose over 3 days (infant age not reported) did not report on the safety of iron sucrose in breastfed infants; however adverse reactions in breastfed infants were not reported.

Clinical Considerations

Monitor breastfed infants for gastrointestinal toxicity (constipation, diarrhea).

8.4 Pediatric Use

Safety and effectiveness of iron sucrose for iron replacement treatment in pediatric patients with dialysis-dependent or non-dialysis-dependent CKD have not been established.

Safety and effectiveness of iron sucrose for iron maintenance treatment in pediatric patients 2 years of age and older with dialysis-dependent or non-dialysis-dependent CKD receiving erythropoietin therapy were studied. Iron sucrose at doses of 0.5 mg/kg, 1 mg/kg, and 2 mg/kg was administered. All three doses maintained hemoglobin between 10.5 g/dL and 14.0 g/dL in about 50% of subjects over the 12-week treatment period with stable EPO dosing *[see Clinical Studies (14.7)]*.

Iron sucrose has not been studied in patients younger than 2 years of age.

In a country where iron sucrose is available for use in children, at a single site, five premature infants (weight less than 1,250 g) developed necrotizing enterocolitis and two of the five died during or following a period when they received iron sucrose, several other medications and erythropoietin. Necrotizing enterocolitis may be a complication of prematurity in very low birth weight infants. No causal relationship to iron sucrose or any other drugs could be established.

8.5 Geriatric Use

Of the 1,051 patients in two post-marketing safety studies of iron sucrose, 40% were 65 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In general, dose administration to an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE

No data are available regarding overdosage of iron sucrose in humans. Excessive dosages of iron sucrose may lead to accumulation of iron in storage sites potentially leading to hemosiderosis. Do not administer iron sucrose to patients with iron overload *[see Warnings and Precautions (5.3)]*. Iron sucrose is not dialyzable through CA210 (Baxter) High Efficiency or Fresenius F80A High Flux dialysis membranes.

Toxicities in single-dose studies in mice and rats, at intravenous iron sucrose doses up to 8 times the maximum recommended human dose based on body surface area, included sedation, hypoactivity, pale eyes, bleeding in the gastrointestinal tract and lungs, and mortality.

11 DESCRIPTION

Iron sucrose injection, USP, an iron replacement product, is a brown, sterile, aqueous, complex of polynuclear iron (III)-hydroxide in sucrose for intravenous use. Iron sucrose injection has a molecular weight of approximately 34,000 to 60,000 daltons and a proposed structural formula:

$[Na_2Fe_5O_8(OH) \cdot 3(H_2O)]_n \cdot m(C_{12}H_{22}O_{11})$ where: n is the degree of iron polymerization and m is the number of sucrose molecules associated with the iron (III)-hydroxide.

Each mL contains 20 mg elemental iron as iron sucrose in water for injection. Iron sucrose injection is available in 10 mL single-dose vials (200 mg elemental iron per 10 mL), 5 mL single-dose vials (100 mg elemental iron per 5 mL), and 2.5 mL single-dose vials (50 mg elemental iron per 2.5 mL). The drug product contains approximately 30% sucrose w/v (300 mg/mL) and sodium chloride for tonicity. Sodium hydroxide may be added to adjust pH to 10.5 to 11.1. The product contains no preservatives. The osmolarity of the injection is 1,250 mOsmol/L.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Iron sucrose is an aqueous complex of poly-nuclear iron (III)-hydroxide in sucrose. Following intravenous administration, Iron sucrose is dissociated into iron and sucrose and the iron is transported as a complex with transferrin to target cells including erythroid precursor cells. The iron in the precursor cells is incorporated into hemoglobin as the cells mature into red blood cells.

12.2 Pharmacodynamics

Following intravenous administration, iron sucrose is dissociated into iron and sucrose. In 22 patients undergoing hemodialysis and receiving erythropoietin (recombinant human erythropoietin) therapy treated with iron sucrose containing 100 mg of iron, three times weekly for three weeks, significant increases in serum iron and serum ferritin and significant decreases in total iron binding capacity occurred four weeks from the initiation of iron sucrose treatment.

12.3 Pharmacokinetics

In healthy adults administered intravenous doses of iron sucrose, its iron component exhibited first order kinetics with an elimination half-life of 6 h, total clearance of 1.2 L/h, and steady state apparent volume of distribution of 7.9 L. The iron component appeared to distribute mainly in blood and to some extent in extravascular fluid. A study evaluating iron sucrose containing 100 mg of iron labeled with $^{52}Fe/^{59}Fe$ in patients with iron deficiency showed that a significant amount of the administered iron is distributed to the liver, spleen and bone marrow and that the bone marrow is an irreversible iron trapping compartment.

Following intravenous administration of iron sucrose, iron sucrose is dissociated into iron and sucrose. The sucrose component is eliminated mainly by urinary excretion. In a study evaluating a single intravenous dose of iron sucrose containing 1,510 mg of sucrose and 100 mg of iron in 12 healthy adults (9 female, 3 male: age range 32 to 52), 68.3% of the sucrose was eliminated in urine in 4 h and 75.4% in 24 h. Some iron was also eliminated in the urine. Neither transferrin nor transferrin receptor levels changed immediately after the dose administration. In this study and another study evaluating a single intravenous dose of iron sucrose containing 500 to 700 mg of iron in 26 patients with anemia on erythropoietin therapy (23 female, 3 male; age range 16 to 60), approximately 5% of the iron was eliminated in urine in 24 h at each dose level. The effects of age and gender on the pharmacokinetics of iron sucrose have not been studied.

Pharmacokinetics in Pediatric Patients

In a single-dose PK study of iron sucrose, patients with NDD-CKD ages 12 to 16 (N=11) received intravenous bolus doses of iron sucrose at 7 mg/kg (maximum 200 mg) administered over 5 minutes. Following a single dose of iron sucrose, the half-life of total serum iron was 8 hours. The mean C_{max} and AUC values were 8545 mcg/dL and 31305 hr•mcg/dL, respectively, which were 1.42- and 1.67-fold higher than dose adjusted adult C_{max} and AUC values.

Iron sucrose is not dialyzable through CA210 (Baxter) High Efficiency or Fresenius F80A High Flux dialysis membranes. In *in vitro* studies, the amount of iron sucrose in the dialysate fluid was below the levels of detection of the assay (less than 2 parts per million).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with iron sucrose.

Iron sucrose was not mutagenic *in vitro* in the bacterial reverse mutation assay (Ames test) or the mouse lymphoma assay. Iron sucrose was not clastogenic in the *in vitro* chromosome aberration assay using human lymphocytes or in the *in vivo* mouse micronucleus assay.

Iron sucrose at intravenous doses up to 15 mg/kg/day of elemental iron (1.2 times the maximum recommended human dose based on body surface area) had no effect on fertility and reproductive function of male and female rats.

14 CLINICAL STUDIES

14.1 Clinical Studies Overview

Five clinical trials involving 647 adult patients and one clinical trial involving 131 pediatric patients were conducted to assess the safety and efficacy of iron sucrose.

14.2 Study A: Hemodialysis Dependent-Chronic Kidney Disease (HDD–CKD)

Study A was a multicenter, open-label, historically-controlled study in 101 patients with HDD-CKD (77 patients with iron sucrose treatment and 24 in the historical control group) with IDA. Eligibility criteria for iron sucrose treatment included patients undergoing chronic hemodialysis, receiving erythropoietin, hemoglobin level between 8.0 and 11.0 g/dL, transferrin saturation less than 20%, and serum ferritin less than 300 ng/mL. The mean age of the patients was 65 years with the age range of 31 to 85 years. Of the 77 patients, 44 (57%) were male and 33 (43%) were female.

Iron sucrose 100 mg was administered at 10 consecutive dialysis sessions either as slow injection or a slow infusion. The historical control population consisted of 24 patients with similar ferritin levels as patients treated with iron sucrose, who were off intravenous iron for at least 2 weeks and who had received erythropoietin therapy with hematocrit averaging 31 to 36 for at least two months prior to study entry. The mean age of patients in the historical control group was 56 years, with an age range of 29 to 80 years. Patient age and serum ferritin level were similar between treatment and historical control patients.

Patients in the iron sucrose treated population showed a greater increase in hemoglobin and hematocrit than did patients in the historical control population. See **Table 2**.

Table 2. Changes from Baseline in Hemoglobin and Hematocrit

Efficacy parameters	End of treatment		2 week follow-up		5 week follow-up	
	Iron Sucrose (n=69)	Historical Control (n=18)	Iron Sucrose (n=73)	Historical Control (n=18)	Iron Sucrose (n=71)	Historical Control (n=15)
Hemoglobin (g/dL)	1.0 ± 0.12**	0.0 ± 0.21	1.3 ± 0.14**	-0.6 ± 0.24	1.2 ± 0.17*	-0.1 ± 0.23
Hematocrit (%)	3.1 ± 0.37**	-0.3 ± 0.65	3.6 ± 0.44**	-1.2 ± 0.76	3.3 ± 0.54	0.2 ± 0.86

**p<0.01 and *p<0.05 compared to historical control from ANCOVA analysis with baseline hemoglobin, serum ferritin and erythropoietin dose as covariates.

Serum ferritin increased at endpoint of study from baseline in the iron sucrose-treated population (165.3 ± 24.2 ng/mL) compared to the historical control population (-27.6 ± 9.5 ng/mL). Transferrin saturation also increased at endpoint of study from baseline in the iron sucrose-treated population (8.8 ± 1.6%) compared to this historical control population (-5.1 ± 4.3%).

14.3 Study B: Hemodialysis Dependent-Chronic Kidney Disease (HDD-CKD)

Study B was a multicenter, open label study of iron sucrose in 23 patients with iron deficiency and HDD-CKD who had been discontinued from iron dextran due to intolerance. Eligibility criteria were otherwise identical to Study A. The mean age of the patients in this study was 53 years, with ages ranging from 21 to 79 years. Of the 23 patients enrolled in the study, 10 (44%) were male and 13 (56%) were female.

All 23 enrolled patients were evaluated for efficacy. Increases in mean hemoglobin (1.1 ± 0.2 g/dL), hematocrit (3.6 ± 0.6%), serum ferritin (266.3 ± 30.3 ng/mL) and transferrin saturation (8.7 ± 2.0%) were observed from baseline to end of treatment.

14.4 Study C: Hemodialysis Dependent-Chronic Kidney Disease (HDD-CKD)

Study C was a multicenter, open-label study in patients with HDD-CKD. This study enrolled patients with a hemoglobin less than or equal to 10 g/dL, a serum transferrin saturation less than or equal to 20%, and a serum ferritin less than or equal to 200 ng/mL, who were undergoing maintenance hemodialysis 2 to 3 times weekly. The mean age of the patients enrolled in this study was 41 years, with ages ranging from 16 to 70 years. Of 130 patients evaluated for efficacy in this study, 68 (52%) were male and 62 (48%) were female. Forty-eight percent of the patients had previously been treated with oral iron. Exclusion criteria were similar to those in studies A and B. Iron sucrose was administered in doses of 100 mg during sequential dialysis sessions until a pre-determined (calculated) total dose of iron was administered. A 50 mg dose (2.5 mL) was given to patients within two weeks of study entry as a test dose. Twenty-seven patients (20%) were receiving erythropoietin treatment at study entry and they continued to receive the same erythropoietin dose for the duration of the study.

The modified intention-to-treat (mITT) population consisted of 131 patients. Increases from baseline in mean hemoglobin (1.7 g/dL), hematocrit (5%), serum ferritin (434.6 ng/mL), and serum transferrin saturation (14%) were observed at week 2 of the observation period and these values remained increased at week 4 of the observation period.

14.5 Study D: Non-Dialysis Dependent-Chronic Kidney Disease (NDD-CKD)

Study D (NCT00236977) was a randomized, open-label, multicenter, active-controlled study of the safety and efficacy of oral iron versus iron sucrose in patients with NDD-CKD with or without erythropoietin therapy. Erythropoietin therapy was stable for 8 weeks prior to randomization. In the study 188 patients with NDD-CKD, hemoglobin of ≤11.0 g/dL, transferrin saturation ≤25%, ferritin ≤300 ng/mL were randomized to receive oral iron (325 mg ferrous sulfate three times daily for 56 days); or iron sucrose (either 200 mg over 2 to 5 minutes 5 times within 14 days or two 500 mg infusions on Day 1 and Day 14, administered over 3.5 to 4 hours). The mean age of the 91 treated patients in the iron sucrose group was 61.6 years (range 25 to 86 years) and 64 years (range 21 to 86 years) for the 91 patients in the oral iron group.

A statistically significantly greater proportion of iron sucrose subjects (35/79; 44.3%) compared to oral iron subjects (23/82; 28%) had an increase in hemoglobin ≥1 g/dL at anytime during the study (p=0.03).

14.6 Study E: Peritoneal Dialysis Dependent-Chronic Kidney Disease (PDD-CKD)

Study E (NCT00236938) was a randomized, open-label, multicenter study comparing patients with PDD-CKD receiving an erythropoietin and intravenous iron to patients with PDD-CKD receiving an erythropoietin alone without iron supplementation. Patients with PDD-CKD, stable erythropoietin for 8 weeks, hemoglobin of ≤11.5 g/dL, TSAT ≤25%, ferritin ≤500 ng/mL were randomized to receive either no iron or iron sucrose (300 mg in 250 mL 0.9% NaCl over 1.5 hours on Day 1 and 15 and 400 mg in 250 mL 0.9% NaCl over 2.5 hours on Day 29). The mean age of the 75 treated patients in the iron sucrose / erythropoietin group was 51.9 years (range 21 to 81 years) vs. 52.8 years (range 23 to 77 years) for 46 patients in the erythropoietin alone group.

Patients in the iron sucrose / erythropoietin group had statistically significantly greater mean change from baseline to the highest hemoglobin value (1.3 g/dL), compared to subjects who received erythropoietin alone (0.6 g/dL) (p<0.01). A greater proportion of subjects treated with iron sucrose / erythropoietin (59.1 %) had an increase in hemoglobin of ≥1 g/dL at any time during the study compared to the subjects who received erythropoietin only (33.3%).

14.7 Study F: Iron Maintenance Treatment Dosing in Pediatric Patients Ages 2 Years and Older with Chronic Kidney Disease

Study F (NCT00239642) was a randomized, open-label, dose-ranging study for iron maintenance treatment in pediatric patients with dialysis-dependent or non-dialysis-dependent CKD on stable erythropoietin therapy. The study randomized patients to one of three doses of iron sucrose (0.5 mg/kg, 1 mg/kg or 2 mg/kg). The mean age was 13 years (range 2 to 20 years). Over 70% of patients were 12 years or older in all three groups. There were 84 males and 61 females. About 60% of patients underwent hemodialysis and 25% underwent peritoneal dialysis in all three dose groups. At baseline, the mean

hemoglobin was 12 g/dL, the mean TSAT was 33% and the mean ferritin was 300 ng/mL. Patients with HDD-CKD received iron sucrose once every other week for 6 doses. Patients with PDD-CKD or NDD-CKD received iron sucrose once every 4 weeks for 3 doses. Among 131 evaluable patients with stable erythropoietin dosing, the proportion of patients who maintained hemoglobin between 10.5 g/dL and 14.0 g/dL during the 12-week treatment period was 58.7%, 46.7%, and 45.0% in the iron sucrose 0.5 mg/kg, 1 mg/kg, and 2 mg/kg groups, respectively. A dose-response relationship was not demonstrated.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Iron sucrose injection, USP is a brown, sterile, aqueous injection supplied in sterile 2.5 mL, 5 mL, and 10 mL single-dose vials. Each 2.5 mL vial contains 50 mg elemental iron, each 5 mL vial contains 100 mg elemental iron and each 10 mL vial contains 200 mg elemental iron (20 mg/mL). Discard unused portion.

NDC 0781-3485-95	50 mg/2.5 mL Single-Dose Vial	Packages of 10
NDC 0781-3485-96	50 mg/2.5 mL Single-Dose Vial	Packages of 25
NDC 0781-3486-95	100 mg/5 mL Single-Dose Vial	Packages of 10
NDC 0781-3486-96	100 mg/5 mL Single-Dose Vial	Packages of 25
NDC 0781-3487-14	200 mg/10 mL Single-Dose Vial	Packages of 5
NDC 0781-3487-92	200 mg/10 mL Single-Dose Vial	Packages of 10

16.2 Stability and Storage

Contains no preservatives. Store in original carton at 20°C to 25°C (68° F to 77° F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not freeze.

Syringe Stability: Iron sucrose injection, when diluted with 0.9% NaCl at concentrations ranging from 2 mg to 10 mg of elemental iron per mL, or undiluted (20 mg elemental iron per mL) and stored in a plastic syringe, was found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C) and under refrigeration (4°C ± 2°C).

Intravenous Admixture Stability: Iron sucrose injection, when added to intravenous infusion bags (PVC or non-PVC) containing 0.9% NaCl at concentrations ranging from 1 mg to 2 mg of elemental iron per mL, has been found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C).

Do not dilute to concentrations below 1 mg/mL.

Do not mix iron sucrose injection with other medications or add to parenteral nutrition solutions for intravenous infusion.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to infusion.

17 PATIENT COUNSELING INFORMATION

Prior History of Reactions to Parenteral Iron Products

Question patients regarding any prior history of reactions to parenteral iron products *[see Warnings and Precautions (5)]*.

Serious Hypersensitivity Reactions

Advise patients to report any symptoms of hypersensitivity that may develop during and following iron sucrose injection administration, such as rash, itching, dizziness, light-headedness, swelling, and breathing problems *[see Warnings and Precautions (5)]*.

Manufactured by Rafarm S.A. for
Sandoz Inc., Princeton, NJ 08540

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 212340

LABELING REVIEW(s)

Labeling Review
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	06/04/2025, 08/04/2025
ANDA Number(s)	212340
Review Number	5 Addendum (b)(4) (b)(4) updated cover page to included additional submission dates; (b)(4)
Applicant Name	Sandoz Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Iron Sucrose Injection USP, 50 mg Elemental Iron/2.5 mL (20 mg/mL), 100 mg Elemental Iron/5 mL (20 mg/mL), 200 mg Elemental Iron/10 mL (20 mg/mL) (Single-Dose Vials)
Proposed Proprietary Name	N/A
Submission Received Date	May 27, 2025, June 17, 2025, June 9, 2025, June 11, 2025
Primary Labeling Reviewer	Cameron Clark
Secondary Labeling Reviewer	Ellen Hwang

Review Conclusion
☒ Acceptable - No Comments
☐ Acceptable - Include Post Approval Comments
☐ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant
☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant

On Drug Product Alert List	☒ Yes	☐ No
Acceptable For Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No

TABLE OF CONTENTS

1 LABELING COMMENTS (C5 ADDENDUM)

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C5 ADDENDUM)

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C5 ADDENDUM)

The Division of Labeling has no further questions/comments at this time based on your labeling submission received May 27, 2025, June 17, 2025, June 9, 2025, June 11, 2025.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST-APPROVAL REVISIONS (C5 ADDENDUM)

These comments will be addressed post approval (in the first labeling supplement review).

2 INSTRUCTIONS FOR ASSESSMENT (C5 ADDENDUM)

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

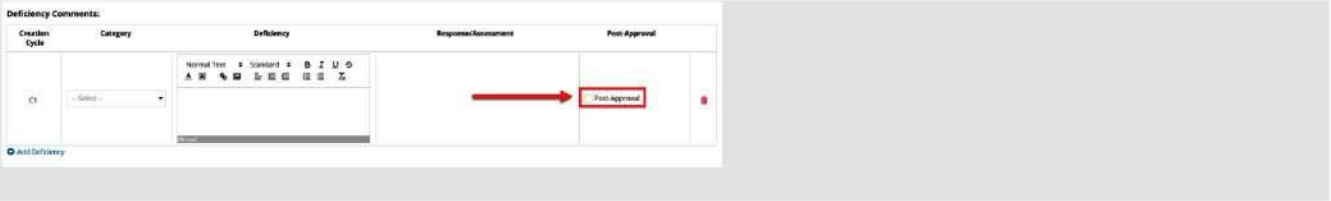
If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:
Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the DLR Standardized Comments SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.



3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C5 ADDENDUM)

Table 1: Review Summary of Container Label and Carton Labeling				
	Final or Draft or N/A	**Packaging Sizes**	**Submission Received Date(s)**	**Recommendation**
Container	Final	50 mg/2.5 mL (20 mg/mL) single dose vials 100 mg/5 mL (20 mg/mL) single dose vials 200 mg/10 mL (20 mg/mL) single dose vials	06/17/2025	Satisfactory
Blister	N/A	N/A		
Carton	Final	50 mg/2.5 mL (20 mg/mL) single dose vials: cartons of 10s and 25s 100 mg/5 mL (20 mg/mL) single dose vials: cartons of 10s and 25s 200 mg/10 mL single dose vials: cartons of 5s and 10s	06/17/2025	Satisfactory

Table 2: Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or N/A	**Revision Date and/or Code**	**Submission Received Date(s)**	**Recommendation**
Prescribing Information	Draft	Revised: 06/2025	06/17/2025	Satisfactory
Medication Guide	N/A	N/A		
Patient Information	N/A	N/A		
Instructions for Use	N/A	N/A		

4 LABELING REVIEW INFORMATION(C5 ADDENDUM)

4.1 REGULATORY INFORMATION (C5 ADDENDUM)

Yes	No	
☐	☒	Are there any applicable issues in DLR's SharePoint Drug Facts ?
☒	☐	Is the drug product listed in the OGD Drug Product Alert List (OGD DPAL) on OGD's SharePoint? (b)(2)

Yes	No	
		(b)(2)

CP	FDA-2005-P-0319 (2005P-0095)	Venofer	ferric oxyhydroxide (iron sucrose)	Requests FDA to require identical manufacturing process, physico-chemical properties, BE standards		021135	
No Approval Actions (TA/AP) can be taken prior to contacting Policy Lead		No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL for Bioequivalence, Filing, Labeling or Quality prior to contacting Policy Lead		On July 1, 2024, the Agency published a memorandum stating that the Center for Drug Evaluation and Research (CDER) "is reevaluating its determination that the active ingredient of the iron products subject to the May 26, 2021, Citizen Petition response is ferric oxyhydroxide." The memorandum also stated that during the reevaluation period, "CDER is accepting the active ingredient names as approved prior to the May 26, 2021, Citizen Petition response for all iron products subject to the May 26, 2021, Citizen Petition response..." (See Docket Nos FDA-2016-P-1163 and FDA-2021-P-0893, available at regulations.gov.) Please contact Policy prior to issuing an Approval Action (TA/AP), or correspondence (e.g., CRL/DRL/IR), for ANDAs 209712, 211386, 211411, 212276, 218226.	3/9/2005	Geeta Daniel

CP	FDA-2021-P-0893	Multiple iron products: Velphoro, Venofer, Ferrlecit, INFeD, Dexferrum, Imferon, Proferdex	multiple: ferric oxyhydroxide	Petitioner request that the FDA reverse certain actions announced in its Citizen Petition Response dated May 26, 2021, FDA-2016-P-1163 (Response). In the Response, the Agency principally determined that the solid oral tablet Velphoro® (sucroferric oxyhydroxide) is not entitled to new chemical entity (NCE) exclusivity. Vifor offers no opinion on that issue. However, Vifor strongly disputes those portions of the Response that purport to change the established names and active ingredients of Velphoro and several IV iron products, including Venofer, to "ferric oxyhydroxide." Vifor also challenges the actions FDA has taken to implement that change in Drugs@FDA and the Orange Book.			
205169, 021135, 020955, 017641, 040024, 010787, 017807		No Approval Actions (TA/AP) can be issued prior to contacting Policy Lead	No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL for Bioequivalence, Filing, Labeling or Quality prior to contacting Policy Lead	On July 1, 2024, the Agency published a memorandum stating that the Center for Drug Evaluation and Research (CDER) "is reevaluating its determination that the active ingredient of the iron products subject to the May 26, 2021, Citizen Petition response is ferric oxyhydroxide." The memorandum also stated that during the reevaluation period, "CDER is accepting the active ingredient names as approved prior to the May 26, 2021, Citizen Petition response for all iron products subject to the May 26, 2021, Citizen Petition response..." (See Docket Nos FDA-2016-P-1163 and FDA-2021-P-0893, available at regulations.gov.) Please contact Policy prior to issuing an Approval Action (TA/AP), or correspondence (e.g., CRL/DRL/IR), for ANDAs 209712, 211386, 211411, 212276, 218226.	8/12/2021	Geeta Daniel

(b)(2)

4.2 MODEL PRESCRIBING INFORMATION (C5 ADDENDUM)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): NDA021135 / S-038

Supplement Approval Date: 08/01/2024

Proprietary Name: Venofer Injection

Established Name: Iron Sucrose Injection USP

Description of Supplement:

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)
Please refer to your supplemental new drug application (sNDA) dated and received June 10, 2022, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Venofer (iron sucrose) injection. We also refer to our letter dated May 11, 2022, requesting you submit draft labeling for your Prescribing Information in accordance with the requests below: In Section 6.2 add the following information (additions are shown as underlined text and deletions are shown as strikethroughs): • ~~Cardiac disorders: bradycardia~~ • ~~Vascular disorders: shock~~ • Cardiovascular System: bradycardia, shock, acute myocardial ischemia with or without myocardial infarction or with in-stent thrombosis in the context of a hypersensitivity reaction. This "Changes Being Effected" sNDA provides for these requested changes. Link: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8075ccca
☐ MOST RECENTLY APPROVED ANDA MODEL LABELING
☒ OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out): S-040 and S-041 are CMC supplements approved after the model labeling that did not have an impact on labeling.

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is **up-to-date** with the RLD/Model labeling.

Reviewer Comments:

Cycle 3 Addendum Update 08/26/2021:

Internal

(b)(2)

Cycle 4 Update 03/18/2025:

ANDA labeling is modeled after the RLD's S-038 labeling

The following deficiency was included in the Cycle 3 addendum review:
GENERAL COMMENTS: We acknowledge receipt of your amendment received on December 28, 2020, which was deferred per 21 CFR 314.110 and not reviewed for this action. You may incorporate applicable sections of the deferred amendment by specific reference as part of your response to the deficiencies cited in this letter.

On 04/17/2023, the application received a complete response letter (CRL) due to drug substance, drug product, and bioequivalence deficiencies. Our labeling deficiency was also included in the CRL. On 08/18/2023, the Applicant provided their complete response to the deficiencies included in the CRL. On 04/04/2024 the Applicant submitted revised labeling to be same as the RLD updated labeling. Furthermore, on 08/05/2024, the Applicant submitted revised labeling to (b)(4) (b)(4) (b)(4) to align the labeling with the most recently approved RLD labeling.

Cycle 4 Addendum Update 05/19/2025:
On 05/19/2025, OGDP provided the following language to incorporate to be conveyed to the Applicant. We have included the language as a general comment for the Applicant below.

On April 15, 2016, Foley Hoag LLP submitted a Citizen Petition (Docket No. FDA-2016-P-1163) requesting, among other things, that FDA recognize that Velphoro (new drug application (NDA) 205109) is eligible for 5-year new chemical entity (NCE) exclusivity under 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (Velphoro Citizen Petition). On May 26, 2021, FDA published a response to the Velphoro Citizen Petition in which we denied the request, among other things, and determined that Velphoro's active moiety and active ingredient are ferric oxyhydroxide.

Following publication of the Velphoro Citizen Petition response, the Agency accordingly issued a revised draft product-specific guidance (PSG), updated the Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book) and Drugs@FDA. Please be advised that the agency intends to consider additional regulatory actions and/or policy changes to address certain issues implicated by this petition response.

Additionally, on August 3, 2021, Vifor (International) Inc., Switzerland (Vifor) submitted a Citizen Petition and Petition for Stay (Docket No. FDA-2021-P-0893) (Vifor Petition) requesting the Agency reverse certain actions announced in its Velphoro Citizen Petition response. The issues raised by the Vifor petition are under review by the Agency, and FDA has not made a final decision on these issues. On July 1, 2024, the Agency published a memorandum stating that the Center for Drug Evaluation and Research (CDER) "is reevaluating its determination that the active ingredient of the iron products subject to the May 26, 2021, Citizen Petition response is ferric oxyhydroxide." The memorandum also stated that during the reevaluation period, "CDER is accepting the active ingredient names as approved prior to the May 26, 2021, Citizen Petition response for all iron products subject to the May 26, 2021, Citizen Petition response..." (See Docket Nos FDA-2016-P-1163 and FDA-2021-P-0893, available at regulations.gov.).

Also note that Sonnenschein, Nath & Rosenthal LLP submitted a Citizen Petition (Docket No. FDA-2005-P-0319) (Venofer Citizen Petition) requesting, among other things, that the FDA adopt and apply certain requirements to ensure "the even-handed application of the requirements of Section 505 of the [FD&C Act] and the safety and efficacy of any generic version or pharmaceutical equivalent" of Venofer (Venofer Citizen Petition, at 2). The issues raised by that petition are under review by the Agency, and the FDA has not made a final decision on these issues.

Cycle 5 Update 06/23/2025:

The following deficiencies were conveyed to the Applicant during the Cycle 4 labeling review:

1. GENERAL COMMENTS

On April 15, 2016, Foley Hoag LLP submitted a Citizen Petition (Docket No. FDA-2016-P-1163) requesting, among other things, that FDA recognize that Velphoro (new drug application (NDA) 205109) is eligible for 5-year new chemical entity (NCE) exclusivity under 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (Velphoro Citizen Petition). On May 26, 2021, FDA published a response to the Velphoro Citizen Petition in which we denied the request, among other things, and determined that Velphoro's active moiety and active ingredient are ferric oxyhydroxide.

Following publication of the Velphoro Citizen Petition response, the Agency accordingly issued a revised draft product-specific guidance (PSG), updated the Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book) and Drugs@FDA. Please be advised that the agency intends to consider additional regulatory actions and/or policy changes to address certain issues implicated by this petition response.

Additionally, on August 3, 2021, Vifor (International) Inc., Switzerland (Vifor) submitted a Citizen Petition and Petition for Stay (Docket No. FDA-2021-P-0893) (Vifor Petition) requesting the Agency reverse certain actions announced in its Velphoro Citizen Petition response. The issues raised by the Vifor petition are under review by the Agency, and FDA has not made a final decision on these issues. On July 1, 2024, the Agency published a memorandum stating that the Center for Drug Evaluation and Research (CDER) "is reevaluating its determination that the active ingredient of the iron products subject to the May 26, 2021, Citizen Petition response is ferric oxyhydroxide." The memorandum also stated that during the reevaluation period, "CDER is accepting the active ingredient names as approved prior to the May 26, 2021, Citizen Petition response for all iron products subject to the May 26, 2021, Citizen Petition response..." (See Docket Nos FDA-2016-P-1163 and FDA-2021-P-0893, available at regulations.gov.).

Also note that Sonnenschein, Nath & Rosenthal LLP submitted a Citizen Petition (Docket No. FDA-2005-P-0319) (Venofer Citizen Petition) requesting, among other things, that the FDA adopt and apply certain requirements to ensure "the even-handed application of the requirements of Section 505 of the [FD&C Act] and the safety and efficacy of any generic version or pharmaceutical equivalent" of Venofer (Venofer Citizen Petition, at 2). The issues raised by that petition are under review by the Agency, and the FDA has not made a final decision on these issues.

2. CONTAINER LABEL

a. Decrease the prominence of the net quantity statement (i.e., 2.5 mL Single-Dose Vial, 5 mL Single-Dose Vial, 10 mL Single-Dose Vial) on all container labels so that it does not compete with the most critical information (e.g., established name, strength, route of administration, etc.), on the principal display panel (PDP). Refer to the Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors | FDA.

b. Revise the route of administration to title case (i.e., "For Intravenous Use Only") to be same as the RLD.

3. CARTON LABELING

a. Side Panel: Add the word "Sterile" following the storage temperatures on all carton labeling to be same as the RLD.
b. Side Panel: Revise [redacted] to "Sodium hydroxide may be added to adjust pH to 10.5 to 11.1." on all carton labeling to be same as the RLD.
c. Refer to the comment under 1b.

4. PRESCRIBING INFORMATION

a. HOW SUPPLIED/STORAGE AND HANDLING: Add the "USP" descriptor to the HOW SUPPLIED/STORAGE AND HANDLING section.
b. HOW SUPPLIED/ STORAGE AND HANDLING: Add your product description (e.g., shape, color, scoring, coating, and imprint code) to be in accordance with the information in your submission, as required per 21 CFR 201.57(c)(17).
c. HOW SUPPLIED/STORAGE AND HANDLING: Add "Discard unused portion" to this section as the proposed product is for a single-dose container. Refer to the Guidance for Industry - Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Container for Human Use.

On 05/27/2025, the Applicant submitted revised labeling to address our deficiencies. Furthermore, on 06/05/2025, the following Discipline Review Letter (DRL) (Quality's Recommendation) was sent to the Applicant:

LABELING

We recommend you [redacted]

(b)(4)

On 06/11/2025, the Applicant submitted revised labeling to address the DRL. However, the Applicant included [redacted] on all labels in labeling. Therefore, on 06/16/2025, we sent the following Information Request (IR) to the Applicant:

We are currently reviewing the labeling for ANDA 212340, and the review team has the following comments: We acknowledge your container labels, carton labeling and Prescribing Information submitted on June 11, 2025. We request that you revise [redacted] **to "… and sodium chloride for tonicity." on all labels and labeling and resubmit for our review**

On 06/17/2025, the Applicant provided the following response to our IR:

Sandoz has revised the statement on the container/carton labeling and prescribing information from [redacted] to "… and sodium chloride for tonicity.". The revised labels are provided in Module 1.14.1.1 and prescribing information in Module 1.14.1.3. The annotated comparison to the previously submitted labels and package insert are provided in Module 1.14.1.2 and Module 1.14.3.1, respectively.

Deficiency Comments:

~~Deficiency # 1~~

~~Created in C4 (Addendum)~~

~~General Comments~~

(b)(4)

~~Response / Assessment:~~	(b)(4)

4.3 PATENTS AND EXCLUSIVITIES (C5 ADDENDUM)

The Orange Book was searched on 06/30/2025

Table 4 provides Orange Book patents for the Model Labeling (NDA021135) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	**Patent Number**	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact**
	N/A						

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling						
Strengths	**Exclusivity Code**	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact**
	N/A					

Reviewer Assessment:

Deficiency	**No Deficiency**	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has **expired** and the applicant needs to revise labeling.
Reviewer Comments: **Deficiency Comments:**		

4.4 UNITED STATES PHARMACOPEIA (USP) (C5 ADDENDUM)

The USP was searched on 06/12/2025

Table 6: USP				
	YES or NO	**Date**	**Monograph Title (N/A if no monograph)**	**Packaging and Storage/Labeling Statements (N/A if no monograph)**
Currently Official	Yes		Iron Sucrose Injection	ADDITIONAL REQUIREMENTS Change to read:

Table 6: USP				
	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
				•Packaging and Storage: Preserve in single-dose containers▲ , preferably▲ (RB 1-Apr-2023)of Type I glass. Store at controlled room temperature. Do not freeze. •Labeling: Label it to indicate that it is for intravenous use only, and that when administered by intravenous infusion, the Injection must be diluted with 0.9% Sodium Chloride Injection to a concentration of 1.0–2.0 mg/mL of elemental iron. Label it also to state the total osmolarity of the solution expressed in mOsmol/L.
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	**Established name** is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary **name is different from USP** established name.
☐	☒	**USP descriptor** is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	**DISSOLUTION**: The applicant's dissolution statement is appropriate.
☐	☒	**ORGANIC IMPURITIES**: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	**ASSAY**: Drug product meets USP acceptance criteria for assay.

Reviewer Comments:

Cycle 5 Update 06/23/2025:

The Applicant addressed our deficiency. The revision is acceptable.

Additional Note: **Per internal meeting held on 07/01/2022 and 01/20/2023 between DLR, OPQ, ORP and OGDP, the decision was made to defer the review per 21 CFR 314.110. In addition, additional language was added in this review about existing citizen petition for Venofer [Docket ID: FDA 2005-P-0319]**

(b)(4)

Deficiency Comments:

~~Deficiency # 1~~

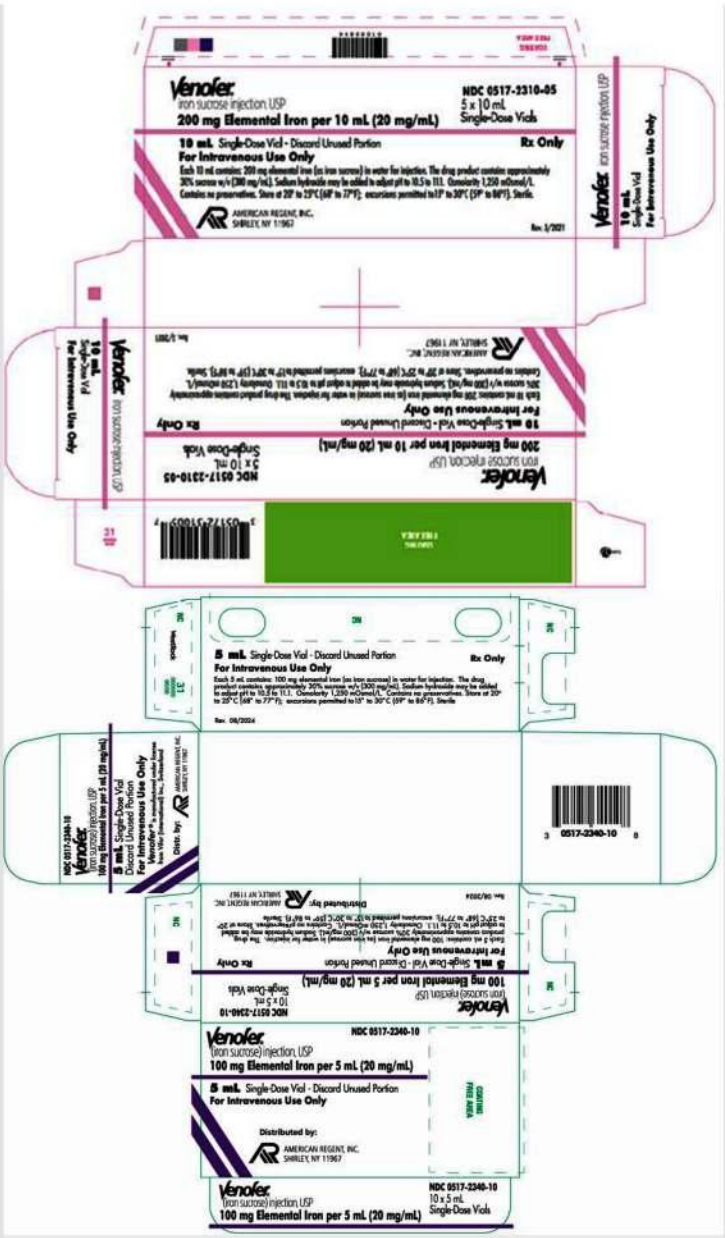
~~Created in C4~~

~~Prescribing Information Response / Assessment:~~

(b)(4)

4.5 MODEL CONTAINER LABELS (C5 ADDENDUM)

Model container/carton/blister labels (Source: carton labeling: ANRPT-21 (submitted on 12/16/2021) and ANRPT-24 (submitted 12/18/2024); container label: ANRPT-20 (submitted on 12/17/2020) **)**


Venofer
iron sucrose injection USP
200 mg Elemental Iron per 10 mL (20 mg/mL)
NDC 0517-2310-05
5 x 10 mL
Single-Dose Vials
10 mL Single-Dose Vial - Discard Unused Portion
Rx Only
For Intravenous Use Only
AMERICAN REGENT, INC.
SHIRLEY, NY 11967
5 mL Single-Dose Vial - Discard Unused Portion
Rx Only
For Intravenous Use Only
NDC 0517-2340-10
100 mg Elemental Iron per 5 mL (20 mg/mL)
10 x 5 mL
Single-Dose Vials
Distributed by:
AMERICAN REGENT, INC.
SHIRLEY, NY 11967
CENTRAL PRICE AREA

5 ASSESSMENT OF ANDA LABELING AND LABELS (C5 ADDENDUM)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C5 ADDENDUM)

5.1.1 DRUG PRODUCT REVIEW (C5 ADDENDUM)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review complete

Comments from C2 Labeling Review
"CHEMISTRY is INADEQAUTE-MAJOR as of this labeling review cycle dated 4/14/2020."

C3 Labeling Review Updates
DP Review (Reference #44536490) is pending. Per the prescreen checklist, "List of Deficiencies: NA."

Cycle 5 Update 06/12/2025:
The Drug Product review was completed in Panorama on 03/22/2024 with no issues for labeling.

CHAPTER IV: LABELING

IQA ANDA Assessment Guide Reference

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

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

Is the drug product subject of a USP monograph? ☒ Yes ☐ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☒ Statement not needed

If NO, what is/are the needed statement(s)? _____

No update in Review #3.

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

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

If "No," explain.

No update in Review #3.

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

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

No update in Review #3.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (MM)	Imprint Code

Send issue to the Labeling assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues:

Issue Description	Issue Reference Number or Link
N/A	N/A

LABELING LIST OF DEFICIENCIES: NONE

5.1.2 DESCRIPTION (C5 ADDENDUM)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	Each mL contains 20 mg elemental iron as iron sucrose in water for injection. Venofer is available in 5 mL single-dose vials (100 mg elemental iron per 5 mL). The drug product contains approximately 30% sucrose w/v (300 mg/mL). Sodium hydroxide may be added to adjust pH to 10.5 to 11.1. The product contains no preservatives. The osmolarity of the injection is 1,250 mOsmol/L.
Previous ANDA Labeling	(b)(4)
	Reviewer Assessment: Applicant added "Sodium hydroxide may be added to adjust pH to 10.5 to 11.1" to be same as the RLD. This statement is also consistent with the quality submission which includes sodium hydroxide as a pH adjuster. Acceptable.
	(b)(4)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Current ANDA Labeling	Each mL contains 20 mg elemental iron as iron sucrose in water for injection. Iron sucrose injection is available in 10 mL single-dose vials (200 mg elemental iron per 10 mL), 5 mL single-dose vials (100 mg elemental iron per 5 mL), and 2.5 mL single-dose vials (50 mg elemental iron per 2.5 mL). The drug product contains approximately 30% sucrose w/v (300 mg/mL) and sodium chloride for tonicity. Sodium hydroxide may be added to adjust pH to 10.5 to 11.1. The product contains no preservatives. The osmolarity of the injection is 1,250 mOsmol/L. Cycle 5 Update 06/23/2025: Applicant added "and sodium chloride for tonicity" in response to the 6/5/2025 DRL (Quality's Recommendations) and 6/16/2025 IR. Acceptable.

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C5 ADDENDUM)

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	16.1 How Supplied Venofer is supplied sterile in 5 mL single-dose vials. Each 5 mL vial contains 100 mg elemental iron (20 mg/mL). NDC-0517-2340-99 100 mg/5 mL Single-Dose Vial Packages of 10 16.2 Stability and Storage Contains no preservatives. Store in original carton at 20° to 25°C (68° to 77° F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not freeze. Syringe Stability: Venofer, when diluted with 0.9% NaCl at concentrations ranging from 2 mg to 10 mg of elemental iron per mL, or undiluted (20 mg elemental iron per mL) and stored in a plastic syringe, was found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C) and under refrigeration (4°C ± 2°C). Intravenous Admixture Stability: Venofer, when added to intravenous infusion bags (PVC or non-PVC) containing 0.9% NaCl at concentrations ranging from 1 mg to 2 mg of elemental iron per mL, has been found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C). Do not dilute to concentrations below 1 mg/mL. Do not mix Venofer with other medications or add to parenteral nutrition solutions for intravenous infusion. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to infusion.
Previous ANDA Labeling	(b)(4)

Table 8: Comparison of Model Labeling to ANDA Labeling	
	(b)(4)
Current ANDA Labeling	16.1 How Supplied Iron sucrose injection, USP is a brown, sterile, aqueous injection supplied in sterile 2.5 mL, 5 mL, and 10 mL single-dose vials. Each 2.5 mL vial contains 50 mg elemental iron, each 5 mL vial contains 100 mg elemental iron and each 10 mL vial contains 200 mg elemental iron (20 mg/mL). Discard unused portion. NDC 0781-3485-95 50 mg/2.5 mL Single-Dose Vial Packages of 10 NDC 0781-3485-96 50 mg/2.5 mL Single-Dose Vial Packages of 25 NDC 0781-3486-95 100 mg/5 mL Single-Dose Vial Packages of 10 NDC 0781-3486-96 100 mg/5 mL Single-Dose Vial Packages of 25 NDC 0781-3487-14 200 mg/10 mL Single-Dose Vial Packages of 5 NDC 0781-3487-92 200 mg/10 mL Single-Dose Vial Packages of 10 16.2 Stability and Storage Contains no preservatives. Store in original carton at 20°C to 25°C (68° F to 77° F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not freeze. Syringe Stability: Iron sucrose injection, when diluted with 0.9% NaCl at concentrations ranging from 2 mg to 10 mg of elemental iron per mL, or undiluted

Table 8: Comparison of Model Labeling to ANDA Labeling	
	(20 mg elemental iron per mL) and stored in a plastic syringe, was found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C) and under refrigeration (4°C ± 2°C). Intravenous Admixture Stability: Iron sucrose injection, when added to intravenous infusion bags (PVC or non-PVC) containing 0.9% NaCl at concentrations ranging from 1 mg to 2 mg of elemental iron per mL, has been found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C). Do not dilute to concentrations below 1 mg/mL. Do not mix iron sucrose injection with other medications or add to parenteral nutrition solutions for intravenous infusion. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to infusion. Cycle 5 Update 06/23/2025: The Applicant added the product description and discard statement per our request. Acceptable.

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C5 ADDENDUM)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Previous ANDA Labeling	
Name and Address on ANDA Prescribing Information	Manufactured by Rafarm S.A. for Sandoz Inc., Princeton, NJ 08540
Current ANDA Labeling	
Name and Address on ANDA Prescribing Information	Manufactured by Rafarm S.A. for Sandoz Inc., Princeton, NJ 08540 Cycle 5 Update 06/23/2025: No changes -- Acceptable.

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements			
Manufactured by	**Manufactured for**	**Distributed by**	**Distributed for**

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C5 ADDENDUM)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the **too small exemption** [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
ESTABLISHED/PROPRIETARY NAME and STRENGTH:		
☐	☒	**Tall Man** lettering complies with recommendations found on FDA webpage.

Deficiency	No Deficiency	
☐	☒	Established/proprietary **name and strength are the most prominent** information on the Principal Display Panel.
☐	☒	No **intervening text**(written, printed, or graphic matter) between established name and strength.
	THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:	
☐	☒	**Net quantity** statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Dosage** statement.
☐	☒	**NDC number**: prominence, linear bar code, and its orientation.
☐	☒	**Expiration date and lot number** (or placeholder).
☐	☒	**Equivalency statement** (product strength).
☐	☒	**Medication Guide** Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol.
☐	☒	**Image of drug product** represents the true size, color, and imprint.
☐	☒	**Yellow #5** (tartrazine) warning statement is properly displayed.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Latex** warning statement is properly displayed [21 CFR 801.437.].
☐	☒	**Gluten** statement is appropriately stated.
	PRODUCT DIFFERENTIATION:	
☐	☒	ANDA is the **same color** as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple **strengths are differentiated** by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from **related products**.
	STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:	
☐	☒	**Storage/dispensing** statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe **container closure**, cite source, and any issues in Reviewer Comments below.
	OVERALL ASSESSMENT:	
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Cycle 3:

The container labels and carton labeling were found acceptable in the C2 Labeling Review ; however, RLD container labels and carton labeling were revised in NDA 021135/S-037 (see Section 3.3 below). No new deficiencies are identified; thus, the ANDAs previously proposed container labels and carton labeling are satisfactory.

Cycle 4 Update 03/18/2025:

Related Products: Searched "iron sucrose" and "Sandoz" in CDEROne Nexus and did not identify any related products marketed by the Applicant.

Container closure: (b)(4)

(b)(4)

Cycle 5 Update 06/23/2025:

The Applicant addressed all of our Cycle 4 deficiencies as well as the 6/5/2025 DRL (Quality's recommendations) and 6/16/2025 IR. Acceptable.

Additional Note: **Per internal meeting held on 07/01/2022 and 01/20/2023 between DLR, OPQ, ORP and OGDP, the decision was made to defer the review per 21 CFR 314.110. In addition, additional language was added in this review about existing citizen petition for Venofer [Docket ID: FDA 2005-P-0319]. Hence, the applicant revised** (b)(4).

(b)(4)

Deficiency Comments:

~~Deficiency # 1~~

~~Created in C4~~

~~Container Label~~

~~Response / Assessment:~~

(b)(4)

~~Deficiency # 2~~

~~Created in C4~~

~~Container Label~~

~~Response / Assessment:~~

5.2.1 INJECTABLE PRODUCTS (C5 ADDENDUM)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Appropriate **package type term** was used (e.g. multiple-dose, single-dose, single-patient-use).
☐	☒	Product label states, "**Discard unused portion**" for single dose products.
☐	☒	IV, IM, or SC was spelled out.
☐	☒	There is **text on the cap/ferrule** overseal of this injectable product. If "Yes", does the text comply with the recommendations in USP General Chapter <7> Labeling.
☐	☒	The **cap color** is Green for the 50 mg vial and Purple for the 100 mg and 200 mg strength vial . ***NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.***

Reviewer Comments:

Deficiency Comments:

5.2.1.1 CONTAINER LABEL FOR PARENTERAL SOLUTIONS (C5 ADDENDUM)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	**Strength** expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP General Chapter <7> Labeling.
☐	☒	If volume is less than 1 mL, **strength per fraction of a milliliter** is the only expression of strength.
☐	☒	Quantity or proportion of all **inactive ingredients** listed on label as required under 1 CFR 201.100(b)(5)(iii).
☐	☒	Container label includes **instructions for reconstitution** if applicable.
☐	☒	**Aluminum content** is present on immediate container label (SVP, LVP, or PBP) and **warning** is present in the prescribing information.
Reviewer Comments: **Deficiency Comments:**		

5.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING (C5 ADDENDUM)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	**Unit-Dose Carton expression of strength** appropriately stated.
☐	☒	The answers to the Container Label questions are the same for the Carton Labeling. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Cycle 5 Update 06/23/2025:

The Applicant addressed all of our Cycle 4 deficiencies as well as the 6/5/2025 DRL (Quality's recommendations) and the 6/16/2025 IR. Acceptable.

Additional Note: Per internal meeting held on 07/01/2022 and 01/20/2023 between DLR, OPQ, ORP and OGDP, the decision was made to defer the review per 21 CFR 314.110. In addition, additional language was added in this review about existing citizen petition for Venofer [Docket ID: FDA 2005-P-0319]. Hence, the applicant revised (b)(4)

(b)(4)

Deficiency Comments:

~~Deficiency # 1~~

~~Created in C4~~

~~Carton Labeling Response / Assessment:~~

(b)(4)

~~Deficiency # 2~~

~~Created in C4~~

~~Carton Labeling Response / Assessment:~~	
~~Deficiency # 3~~ ~~Created in C4~~ ~~Carton Labeling Response / Assessment:~~	(b)(4)

5.4 PRESCRIBING INFORMATION (C5 ADDENDUM)

Reviewer Assessment:

Deficiency	No Deficiency	
	HIGHLIGHTS:	
☐	☒	**Contact information** for applicant and FDA are listed correctly.
☐	☒	**Revision date** appears at the end of HIGHLIGHTS section (PLR) or end of prescribing information (non-PLR).
	DESCRIPTION/INACTIVE INGREDIENTS:	
	Appropriate **warning/precaution** statements for inactive ingredients are present (21 CFR 201) Check only if applicable:	
☐	☒	☐ Sulfite (21 CFR 201.22) ☐ Yellow #5 (Tartrazine) (21 CFR 201.20) ☐ Phenylalanine/aspartame (21 CFR 201.21) ☐ Latex (21 CFR 801.437).
☐	☒	**Sterile** product statement [21 CFR 201.57(c)(12)(i)(D)].
☐	☒	☐ **Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	☐ **Gluten** statement is appropriately stated.
☐	☒	**Dosage form, pharmacologic/therapeutic class, and route** of administration properly listed [21 CFR 201.57(c)(12)(i)(B)] and[21 CFR 201.57(c)(12)(i)(E)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	All **submitted labels** and labeling are consistent with the HOW SUPPLIED section.
☐	☒	**Physical description** (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	**NDC** numbers are present.
☐	☒	Drug product is the **same color** as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	**Storage or dispensing** statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**"Discard unused portion"** for single-dose products.

Deficiency	No Deficiency	
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
	REGULATORY/OVERALL ASSESSMENT:	
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the **Antiretroviral Pregnancy Registry** (APR) upon full approval.
☐	☒	**Pregnancy registry** information is appropriately included/excluded as required for the RLD.
☐	☒	**Patent/exclusivity** carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Dosage form/strength** carve out (RLD combined labeling): justification for retaining information for safety/efficacy.
☐	☒	Prescribing information meets **formatting requirements** [21 CFR 201.57 (PLR) or 21 CFR 201.80 (non-PLR)].
☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Cycle 5 Update 06/23/2025:

The Applicant addressed all of our Cycle 4 deficiencies as well as the 6/5/2025 DRL (Quality's recommendations) and 6/16/2025 IR. The revised Prescribing Information is acceptable.[1]

Additional Note #1: Per internal meeting held on 07/01/2022 and 01/20/2023 between DLR, OPQ, ORP and OGDP, the decision was made to defer the review per 21 CFR 314.110. In addition, additional language was added in this review about existing citizen petition for Venofer [Docket ID: FDA 2005-P-0319]. Hence, the applicant revised (b)(4)

(b)(4)

Additional Note #2: In reviewing and evaluating this application, DLR has determined the labeling differences proposed by the Applicant, with respect to the listing of sodium chloride as a tonicity agent[2], fall within the "different manufacturers" exception to the same labeling requirement.

Section 505(j)(2)(A)(v) of the FD&C Act requires that an ANDA contain "information to show that the labeling proposed for the new [generic] drug is the same as the labeling approved for the listed drug...except for changes required because of differences approved under a petition filed under [section 505(j)(2)(C) of the FD&C Act] or because the new [generic] drug and the listed drug are produced or distributed by different manufacturers." A parallel provision appears in section 505(j)(4)(G) of the FD&C Act.

Although the requirement set forth in sections 505(j)(2)(A)(v) and 505(j)(4)(G) of the FD&C Act is known as the "same labeling" requirement, it does not require that a generic drug's labeling be identical to that of the listed drug it references in every respect. Section 314.94(a)(8)(iv) sets forth examples of permissible differences in labeling that may result because the generic drug product and

[1] CDER intends to address the regulatory requirement found under 21 CFR 201.100(b)(5)(iii), with respect to tonicity agents (i.e., inactive ingredients "added to adjust the pH or to make the drug isotonic may be declared by name and a statement of their effect") for Venofer.

[2] See 21 CFR 201.100(b)(5)(iii).

RLD are produced or distributed by different manufacturers. Permissible differences include, but are not limited to, the following:
...[D]ifferences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the Federal Food, Drug, and Cosmetic Act.

Therefore, from a labeling perspective, the resulting labeling differences, are permitted exceptions to the same labeling requirement under section 505(j)(2)(A)(v) of the FD&C Act and 21 CFR 314.94(a)(8)(iv), which allow for labeling differences attributable to the products being produced or distributed by different manufacturers.

Deficiency Comments:

~~Deficiency # 1~~

~~Created in C4~~

~~Prescribing Information~~
~~Response / Assessment:~~

~~Deficiency # 2~~

~~Created in C4~~

~~Prescribing Information~~

~~Response / Assessment:~~

(b)(4)

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C5 ADDENDUM)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation

☐	Red #3 (erythrosine)
☐	Yellow #5 (tartrazine)
☒	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:

Comments from C2 Labeling Review

"Questions to the chemist:
Did the firm submit **studies that support** the following found in the Prescribing Information?

Syringe Stability: Iron sucrose injection, when diluted with 0.9% NaCl at concentrations ranging from 2 mg to 10 mg of elemental iron per mL, or undiluted (20 mg elemental iron per mL) and stored in a plastic syringe, was found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C) and under refrigeration (4°C ± 2°C).

Intravenous Admixture Stability: Iron sucrose injection, when added to intravenous infusion bags (PVC or non-PVC) containing 0.9% NaCl at concentrations ranging from 1 mg to 2 mg of elemental iron per mL, has been found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C)."

- **RESPONSE**: "The firm did provide compatibility study data. Please see my assessment of the study on page 52-53 of my DP quality review. The compatibility data is adequate."

Deficiency Comments:

Cameron Clark

Digitally signed by Cameron Clark
Date: 8/04/2025 09:18:52AM
GUID: 5a4fa1f0001c26bc28df0e20df234537

Ellen Hwang

Digitally signed by Ellen Hwang
Date: 8/04/2025 09:20:05AM
GUID: 5256bdc00002af3bc3fa942a9512a891

[redacted]

Labeling Review

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	June 4, 2025
ANDA Number(s)	212340
Review Number	5
Applicant Name	Sandoz Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Iron Sucrose Injection USP, 50 mg Elemental Iron/2.5 mL (20 mg/mL), 100 mg Elemental Iron/5 mL (20 mg/mL), 200 mg Elemental Iron/10 mL (20 mg/mL) (Single-Dose Vials)
Proposed Proprietary Name	N/A
Submission Received Date	May 27, 2025, June 17, 2025
Primary Labeling Reviewer	Cameron Clark
Secondary Labeling Reviewer	Ellen Hwang

Review Conclusion

☒ Acceptable - No Comments
☐ Acceptable - Include Post Approval Comments
☐ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant
☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant

On Policy Alert List	☒ Yes	☐ No
Acceptable For Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No

TABLE OF CONTENTS

1 LABELING COMMENTS (C5)

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C5)

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C5)

The Division of Labeling has no further questions/comments at this time based on your labeling submission received May 27, 2025, June 17, 2025.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST-APPROVAL REVISIONS (C5)

These comments will be addressed post approval (in the first labeling supplement review).

2 INSTRUCTIONS FOR ASSESSMENT (C5)

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:
Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the DLR Standardized Comments SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C5)

Table 1: Review Summary of Container Label and Carton Labeling				
	Final or Draft or N/A	**Packaging Sizes**	**Submission Received Date(s)**	**Recommendation**
Container	Final	50 mg/2.5 mL (20 mg/mL) single dose vials 100 mg/5 mL (20 mg/mL) single dose vials 200 mg/10 mL (20 mg/mL) single dose vials	06/17/2025	Satisfactory
Blister	N/A	N/A		
Carton	Final	50 mg/2.5 mL (20 mg/mL) single dose vials: cartons of 10s and 25s 100 mg/5 mL (20 mg/mL) single dose vials: cartons of 10s and 25s 200 mg/10 mL single dose vials: cartons of 5s and 10s	06/17/2025	Satisfactory

Table 2: Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or N/A	**Revision Date and/or Code**	**Submission Received Date(s)**	**Recommendation**
Prescribing Information	Draft	Revised: 06/2025	06/17/2025	Satisfactory
Medication Guide	N/A	N/A		
Patient Information	N/A	N/A		
Instructions for Use	N/A	N/A		

4 LABELING REVIEW INFORMATION(C5)

4.1 REGULATORY INFORMATION (C5)

Yes	No	
☐	☒	Are there any applicable issues in **DLR's SharePoint Drug Facts** ?
☒	☐	Is the drug product listed in the Policy Alert Tracker on **OGD's SharePoint**?
		(b)(2)

Yes	No	
		(b)(2)

4.2 MODEL PRESCRIBING INFORMATION (C5)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)
☒ MOST RECENTLY APPROVED NDA MODEL LABELING *(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)* **NDA#/Supplement# (S-000 if original):** NDA021135 / S-038 **Supplement Approval Date:** 08/01/2024 **Proprietary Name:** Venofer Injection **Established Name:** Iron Sucrose Injection USP **Description of Supplement:**

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)
Please refer to your supplemental new drug application (sNDA) dated and received June 10, 2022, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Venofer (iron sucrose) injection. We also refer to our letter dated May 11, 2022, requesting you submit draft labeling for your Prescribing Information in accordance with the requests below: In Section 6.2 add the following information (additions are shown as underlined text and deletions are shown as strikethroughs): • ~~Cardiac disorders: bradycardia~~ • ~~Vascular disorders: shock~~ • Cardiovascular System: bradycardia, shock, acute myocardial ischemia with or without myocardial infarction or with in-stent thrombosis in the context of a hypersensitivity reaction. This "Changes Being Effected" sNDA provides for these requested changes. Link: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8075ccca
☐ MOST RECENTLY APPROVED ANDA MODEL LABELING
☒ OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out): S-040 and S-041 are CMC supplements approved after the model labeling that did not have an impact on labeling.

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is **up-to-date** with the RLD/Model labeling.

Reviewer Comments:

Cycle 3 Addendum Update 08/26/2021:

Internal

An internal meeting was held on 07/16/2021 between DLR, OPQ, and OGDP to discuss the implication of Velphoro CP response (Docket No. FDA-2016-P-1163; 5/26/2021) which clarified that the active ingredient for the drug products containing ferric oxyhydroxide (iron(III) oxyhydroxide) and carbohydrate sugars is "Ferric Oxyhydroxide". This determination has so far changed the identity of the active ingredient for the iron carbohydrate drug products in the Orange Book and Drugs@FDA, and therefore the identity of the active ingredient for Venofer has also changed from "Iron Sucrose" to "Ferric Oxyhydroxide" in Orange Book and Drugs@FDA. With further such updates anticipated in the USP and RLD labeling, there will be, among other changes, labeling implication such as with the presentation of the established name, as the generic drug products would need to be consistent with the USP designation and RLD labeling. Therefore, the Agency has determined to defer this review per 21 CFR 314.110 and issue the following comments to the applicant.

GENERAL COMMENTS: We acknowledge receipt of your amendment received on December 28, 2020, which was deferred per 21 CFR 314.110 and not reviewed for this action. You may incorporate applicable sections of the deferred amendment by specific reference as part of your response to the deficiencies cited in this letter.

Cycle 4 Update 03/18/2025:

ANDA labeling is modeled after the RLD's S-038 labeling

The following deficiency was included in the Cycle 3 addendum review:

GENERAL COMMENTS: We acknowledge receipt of your amendment received on December 28, 2020, which was deferred per 21 CFR 314.110 and not reviewed for this action. You may incorporate applicable sections of the deferred amendment by specific reference as part of your response to the deficiencies cited in this letter.

On 04/17/2023, the application received a complete response letter (CRL) due to drug substance, drug product, and bioequivalence deficiencies. Our labeling deficiency was also included in the CRL. On 08/18/2023, the Applicant provided their complete response to the deficiencies included in the CRL. On 04/04/2024 the Applicant submitted revised labeling to be same as the RLD updated labeling. Furthermore, on 08/05/2024, the Applicant submitted revised labeling to (b)(4)

(b)(4)

Cycle 4 Addendum Update 05/19/2025:
On 05/19/2025, OGDP provided the following language to incorporate to be conveyed to the Applicant. We have included the language as a general comment for the Applicant below.

(b)(4)

Cycle 5 Update 06/23/2025:
The following deficiencies were conveyed to the Applicant during the Cycle 4 labeling review:

1. GENERAL COMMENTS

On April 15, 2016, Foley Hoag LLP submitted a Citizen Petition (Docket No. FDA-2016-P-1163) requesting, among other things, that FDA recognize that Velphoro (new drug application (NDA) 205109) is eligible for 5-year new chemical entity (NCE) exclusivity under 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (Velphoro Citizen Petition). On May 26, 2021, FDA published a response to the Velphoro Citizen Petition in which we denied the request, among other things, and determined that Velphoro's active moiety and active ingredient are ferric oxyhydroxide.

Following publication of the Velphoro Citizen Petition response, the Agency accordingly issued a revised draft product-specific guidance (PSG), updated the Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book) and Drugs@FDA. Please be advised that the agency intends to consider additional regulatory actions and/or policy changes to address certain issues implicated by this petition response.

Additionally, on August 3, 2021, Vifor (International) Inc., Switzerland (Vifor) submitted a Citizen Petition and Petition for Stay (Docket No. FDA-2021-P-0893) (Vifor Petition) requesting the Agency reverse certain actions announced in its Velphoro Citizen Petition response. The issues raised by the Vifor petition are under review by the Agency, and FDA has not made a final decision on these issues. On July 1, 2024, the Agency published a memorandum stating that the Center for Drug Evaluation and Research (CDER) "is reevaluating its determination that the active ingredient of the iron products subject to the May 26, 2021, Citizen Petition response is ferric oxyhydroxide." The memorandum also stated that during the reevaluation period, "CDER is accepting the active ingredient names as approved prior to the May 26, 2021, Citizen Petition response for all iron products subject to the May 26, 2021, Citizen Petition response..." (See Docket Nos FDA-2016-P-1163 and FDA-2021-P-0893, available at regulations.gov.).

Also note that Sonnenschein, Nath & Rosenthal LLP submitted a Citizen Petition (Docket No. FDA-2005-P-0319) (Venofer Citizen Petition) requesting, among other things, that the FDA adopt and apply certain requirements to ensure "the even-handed application of the requirements of Section 505 of the [FD&C Act] and the safety and efficacy of any generic version or pharmaceutical equivalent" of Venofer (Venofer Citizen Petition, at 2). The issues raised by that petition are under review by the Agency, and the FDA has not made a final decision on these issues.

2. CONTAINER LABEL

a. Decrease the prominence of the net quantity statement (i.e., 2.5 mL Single-Dose Vial, 5 mL Single-Dose Vial, 10 mL Single-Dose Vial) on all container labels so that it does not compete with the most critical information (e.g., established name, strength, route of administration, etc.), on the principal display panel (PDP). Refer to the Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors | FDA.

b. Revise the route of administration to title case (i.e., "For Intravenous Use Only") to be same as the RLD.

3. CARTON LABELING

a. Side Panel: Add the word "Sterile" following the storage temperatures on all carton labeling to be same as the RLD.
b. Side Panel: Revise [redacted] to "Sodium hydroxide may be added to adjust pH to 10.5 to 11.1." on all carton labeling to be same as the RLD.
c. Refer to the comment under 1b.

4. PRESCRIBING INFORMATION

a. HOW SUPPLIED/STORAGE AND HANDLING: Add the "USP" descriptor to the HOW SUPPLIED/STORAGE AND HANDLING section.
b. HOW SUPPLIED/ STORAGE AND HANDLING: Add your product description (e.g., shape, color, scoring, coating, and imprint code) to be in accordance with the information in your submission, as required per 21 CFR 201.57(c)(17).
c. HOW SUPPLIED/STORAGE AND HANDLING: Add "Discard unused portion" to this section as the proposed product is for a single-dose container. Refer to the Guidance for Industry - Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Container for Human Use.

On 05/27/2025, the Applicant submitted revised labeling to address our deficiencies. Furthermore, on 06/05/2025, the following Discipline Review Letter (DRL) (Quality's Recommendation) was sent to the Applicant:

LABELING

(b)(4)

On 06/11/2025, the Applicant submitted revised labeling to address the DRL. However, the Applicant included (b)(4) on all labels in labeling. Therefore, on 06/16/2025, we sent the following Information Request (IR) to the Applicant:

We are currently reviewing the labeling for ANDA 212340, and the review team has the following comments: We acknowledge your container labels, carton labeling and Prescribing Information submitted on June 11, 2025. We request that you revise (b)(4) to "… and sodium chloride for tonicity." on all labels and labeling and resubmit for our review

On 06/17/2025, the Applicant provided the following response to our IR:

Sandoz has revised the statement on the container/carton labeling and prescribing information from "(b)(4)" to "… and sodium chloride for tonicity.". The revised labels are provided in Module 1.14.1.1 and prescribing information in Module 1.14.1.3. The annotated comparison to the previously submitted labels and package insert are provided in Module 1.14.1.2 and Module 1.14.3.1, respectively.

Deficiency Comments:

Deficiency # 1

Created in C4 (Addendum)

General Comments

On April 15, 2016, Foley Hoag LLP submitted a Citizen Petition (Docket No. FDA-2016-P-1163) requesting, among other things, that FDA recognize that Velphoro (new drug application (NDA) 205109) is eligible for 5-year new chemical entity (NCE) exclusivity under 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (Velphoro Citizen Petition). On May 26, 2021, FDA published a response to the Velphoro Citizen Petition in which we denied the request, among other things, and determined that Velphoro's active moiety and active ingredient are ferric oxyhydroxide.

Following publication of the Velphoro Citizen Petition response, the Agency accordingly issued a revised draft product-specific guidance (PSG), updated the Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book) and Drugs@FDA. Please be advised that the agency intends to consider additional regulatory actions and/or policy changes to address certain issues implicated by this petition response.

Additionally, on August 3, 2021, Vifor (International) Inc., Switzerland (Vifor) submitted a Citizen Petition and Petition for Stay (Docket No. FDA-2021-P-0893) (Vifor Petition) requesting the Agency reverse certain actions announced in its Velphoro Citizen Petition response. The issues raised by the Vifor petition are under review by the Agency, and FDA has not made a final decision on these issues. On July 1, 2024, the Agency published a memorandum stating that the Center for Drug Evaluation and Research (CDER) "is reevaluating its determination that the active ingredient of the iron products subject to the May 26, 2021, Citizen Petition response is ferric oxyhydroxide." The memorandum also stated that during the reevaluation period, "CDER is accepting the active ingredient names as approved prior to the May 26, 2021, Citizen Petition response for all iron products subject to the May 26, 2021, Citizen Petition

Response / Assessment:	response..." (See Docket Nos FDA-2016-P-1163 and FDA-2021-P-0893, available at regulations.gov.). Also note that Sonnenschein, Nath & Rosenthal LLP submitted a Citizen Petition (Docket No. FDA-2005-P-0319) (Venofer Citizen Petition) requesting, among other things, that the FDA adopt and apply certain requirements to ensure "the even-handed application of the requirements of Section 505 of the [FD&C Act] and the safety and efficacy of any generic version or pharmaceutical equivalent" of Venofer (Venofer Citizen Petition, at 2). The issues raised by that petition are under review by the Agency, and the FDA has not made a final decision on these issues. **Applicant Response:** Sandoz acknowledges that FDA has not made a final decision on the issues regarding the above-mentioned citizen petitions. **Assessment:** Acceptable.

4.3 PATENTS AND EXCLUSIVITIES (C5)

The Orange Book was searched on 06/12/2025

Table 4 provides Orange Book patents for the Model Labeling (NDA021135) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
	N/A						

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

Strengths	Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
	N/A					

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has **expired** and the applicant needs to revise labeling.
Reviewer Comments: **Deficiency Comments:**		

4.4 UNITED STATES PHARMACOPEIA (USP) (C5)

The USP was searched on 06/12/2025

Table 6: USP				
	YES or NO	**Date**	**Monograph Title (N/A if no monograph)**	**Packaging and Storage/Labeling Statements (N/A if no monograph)**
Currently Official	Yes		Iron Sucrose Injection	ADDITIONAL REQUIREMENTS Change to read: •Packaging and Storage: Preserve in single-dose containers▲ , preferably▲ (RB 1-Apr-2023)of Type I glass. Store at controlled room temperature. Do not freeze. •Labeling: Label it to indicate that it is for intravenous use only, and that when administered by intravenous infusion, the Injection must be diluted with 0.9% Sodium Chloride Injection to a concentration of 1.0–2.0 mg/mL of elemental iron. Label it also to state the total osmolarity of the solution expressed in mOsmol/L.
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

Deficiency	**No Deficiency**	
☐	☒	**Established name** is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary **name is different from USP** established name.
☐	☒	**USP descriptor** is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	**DISSOLUTION**: The applicant's dissolution statement is appropriate.
☐	☒	**ORGANIC IMPURITIES**: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	**ASSAY**: Drug product meets USP acceptance criteria for assay.
Reviewer Comments: Cycle 5 Update 06/23/2025:		

The Applicant addressed our deficiency. The revision is acceptable.

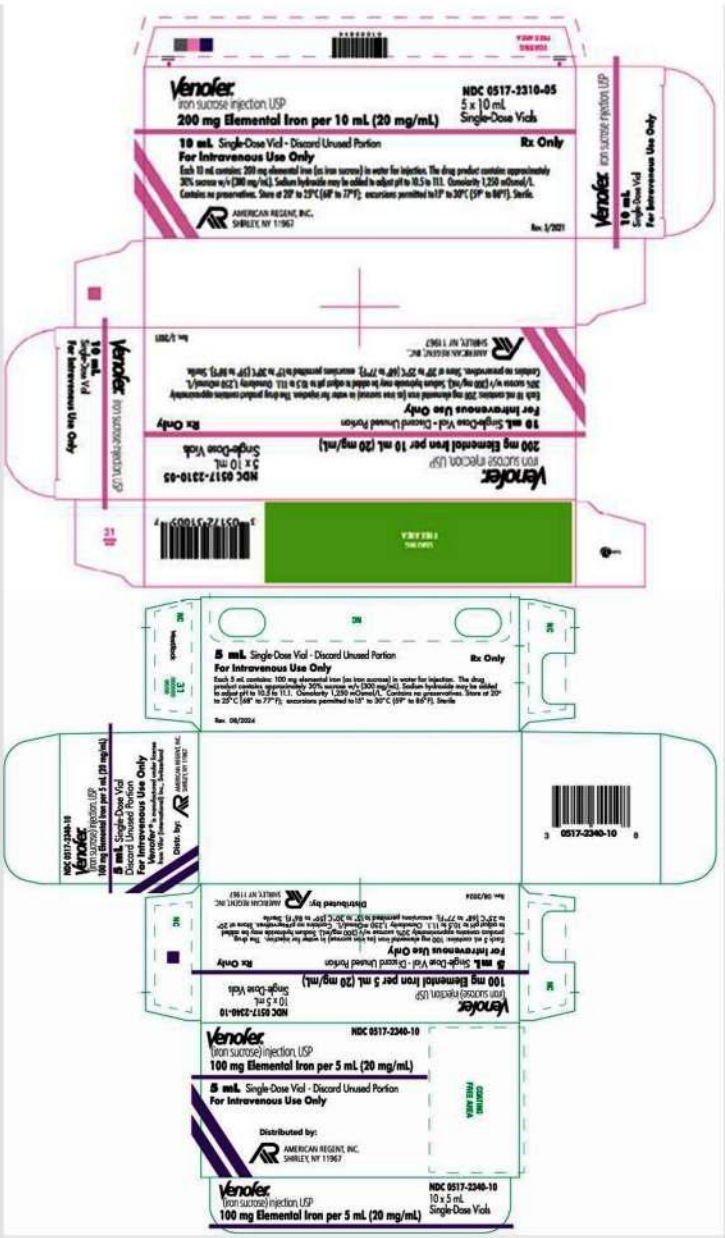
Additional Note: Per internal meeting held on 07/01/2022 and 01/20/2023 between DLR, OPQ, OCC, ORP and OGDP, the decision was made to defer the review per 21 CFR 314.110. In addition, additional language was added in this review about existing citizen petition for Venofer [Docket ID: FDA 2005-P-0319]. Hence, the applicant revised (b)(4)

Deficiency Comments:

Deficiency # 1 Created in C4 Prescribing Information	HOW SUPPLIED/STORAGE AND HANDLING: Add the "USP" descriptor to the HOW SUPPLIED/STORAGE AND HANDLING section.
Response / Assessment:	**Applicant Response:** Sandoz has revised the HOW SUPPLIED/STORAGE AND HANDLING Section of the prescribing information to add "USP," the product description and "Discard unused portion." **Assessment:** Acceptable.

4.5 MODEL CONTAINER LABELS (C5)

Model container/carton/blister labels (Source: carton labeling: ANRPT-21 (submitted on 12/16/2021) and ANRPT-24 (submitted 12/18/2024); container label: ANRPT-20 (submitted on 12/17/2020) **)**


Venofer
iron sucrose injection USP
200 mg Elemental Iron per 10 mL (20 mg/mL)
NDC 0517-2310-05
5 x 10 mL
Single-Dose Vials
10 mL Single-Dose Vial - Discard Unused Portion
Rx Only
For Intravenous Use Only
AMERICAN REGENT, INC.
SHIRLEY, NY 11967
5 mL Single-Dose Vial - Discard Unused Portion
Rx Only
For Intravenous Use Only
100 mg Elemental Iron per 5 mL (20 mg/mL)
NDC 0517-2340-10
10 x 5 mL
Single-Dose Vials
Distributed by:
AMERICAN REGENT, INC.
SHIRLEY, NY 11967
0517-2340-10

5 ASSESSMENT OF ANDA LABELING AND LABELS (C5)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C5)

5.1.1 DRUG PRODUCT REVIEW (C5)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review complete

Comments from C2 Labeling Review
"CHEMISTRY is INADEQAUTE-MAJOR as of this labeling review cycle dated 4/14/2020."

C3 Labeling Review Updates
DP Review (Reference #44536490) is pending. Per the prescreen checklist, "List of Deficiencies: NA."

Cycle 5 Update 06/12/2025:
The Drug Product review was completed in Panorama on 03/22/2024 with no issues for labeling.

CHAPTER IV: LABELING

IQA ANDA Assessment Guide Reference

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

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

Is the drug product subject of a USP monograph? ☒ Yes ☐ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☒ Statement not needed

If NO, what is/are the needed statement(s)? _____

No update in Review #3.

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

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

If "No," explain.

No update in Review #3.

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

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

No update in Review #3.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (MM)	Imprint Code

Send issue to the Labeling assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues:

Issue Description	Issue Reference Number or Link
N/A	N/A

LABELING LIST OF DEFICIENCIES: NONE

5.1.2 DESCRIPTION (C5)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	Each mL contains 20 mg elemental iron as iron sucrose in water for injection. Venofer is available in 5 mL single-dose vials (100 mg elemental iron per 5 mL). The drug product contains approximately 30% sucrose w/v (300 mg/mL). Sodium hydroxide may be added to adjust pH to 10.5 to 11.1. The product contains no preservatives. The osmolarity of the injection is 1,250 mOsmol/L.
Previous ANDA Labeling	(b)(4) **Reviewer Assessment:** Applicant added "Sodium hydroxide may be added to adjust pH to 10.5 to 11.1" to be same as the RLD. This statement is also consistent with the quality submission which includes sodium hydroxide as a pH adjuster. Acceptable. (b)(4)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Current ANDA Labeling	(b)(4)
	Cycle 5 Update 06/23/2025: Applicant added "and sodium chloride for tonicity" in response to the 6/5/2025 DRL (Quality's Recommendations) and 6/16/2025 IR. Acceptable.

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C5)

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	16.1 How Supplied Venofer is supplied sterile in 5 mL single-dose vials. Each 5 mL vial contains 100 mg elemental iron (20 mg/mL). NDC-0517-2340-99 100 mg/5 mL Single-Dose Vial Packages of 10 16.2 Stability and Storage Contains no preservatives. Store in original carton at 20° to 25°C (68° to 77° F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not freeze. Syringe Stability: Venofer, when diluted with 0.9% NaCl at concentrations ranging from 2 mg to 10 mg of elemental iron per mL, or undiluted (20 mg elemental iron per mL) and stored in a plastic syringe, was found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C) and under refrigeration (4°C ± 2°C). Intravenous Admixture Stability: Venofer, when added to intravenous infusion bags (PVC or non-PVC) containing 0.9% NaCl at concentrations ranging from 1 mg to 2 mg of elemental iron per mL, has been found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C). Do not dilute to concentrations below 1 mg/mL. Do not mix Venofer with other medications or add to parenteral nutrition solutions for intravenous infusion. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to infusion.
Previous ANDA Labeling	(b)(4)

Table 8: Comparison of Model Labeling to ANDA Labeling	
	(b)(4)
Current ANDA Labeling	16.1 How Supplied Iron sucrose injection, USP is a brown, sterile, aqueous injection supplied in sterile 2.5 mL, 5 mL, and 10 mL single-dose vials. Each 2.5 mL vial contains 50 mg elemental iron, each 5 mL vial contains 100 mg elemental iron and each 10 mL vial contains 200 mg elemental iron (20 mg/mL). Discard unused portion. NDC 0781-3485-95 50 mg/2.5 mL Single-Dose Vial Packages of 10 NDC 0781-3485-96 50 mg/2.5 mL Single-Dose Vial Packages of 25 NDC 0781-3486-95 100 mg/5 mL Single-Dose Vial Packages of 10 NDC 0781-3486-96 100 mg/5 mL Single-Dose Vial Packages of 25 NDC 0781-3487-14 200 mg/10 mL Single-Dose Vial Packages of 5 NDC 0781-3487-92 200 mg/10 mL Single-Dose Vial Packages of 10 16.2 Stability and Storage Contains no preservatives. Store in original carton at 20°C to 25°C (68° F to 77° F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not freeze. Syringe Stability: Iron sucrose injection, when diluted with 0.9% NaCl at concentrations ranging from 2 mg to 10 mg of elemental iron per mL, or undiluted

Table 8: Comparison of Model Labeling to ANDA Labeling	
	(20 mg elemental iron per mL) and stored in a plastic syringe, was found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C) and under refrigeration (4°C ± 2°C). Intravenous Admixture Stability: Iron sucrose injection, when added to intravenous infusion bags (PVC or non-PVC) containing 0.9% NaCl at concentrations ranging from 1 mg to 2 mg of elemental iron per mL, has been found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C). Do not dilute to concentrations below 1 mg/mL. Do not mix iron sucrose injection with other medications or add to parenteral nutrition solutions for intravenous infusion. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to infusion. Cycle 5 Update 06/23/2025: The Applicant added the product description and discard statement per our request. Acceptable.

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C5)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Previous ANDA Labeling	
Name and Address on ANDA Prescribing Information	Manufactured by Rafarm S.A. for Sandoz Inc., Princeton, NJ 08540
Current ANDA Labeling	
Name and Address on ANDA Prescribing Information	Manufactured by Rafarm S.A. for Sandoz Inc., Princeton, NJ 08540 Cycle 5 Update 06/23/2025: No changes -- Acceptable.

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements			
Manufactured by	**Manufactured for**	**Distributed by**	**Distributed for**

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C5)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the **too small exemption** [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
ESTABLISHED/PROPRIETARY NAME and STRENGTH:		
☐	☒	**Tall Man** lettering complies with recommendations found on FDA webpage.

Deficiency	No Deficiency	
☐	☒	Established/proprietary **name and strength are the most prominent** information on the Principal Display Panel.
☐	☒	No **intervening text**(written, printed, or graphic matter) between established name and strength.
	THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:	
☐	☒	**Net quantity** statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Dosage** statement.
☐	☒	**NDC number**: prominence, linear bar code, and its orientation.
☐	☒	**Expiration date and lot number** (or placeholder).
☐	☒	**Equivalency statement** (product strength).
☐	☒	**Medication Guide** Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol.
☐	☒	**Image of drug product** represents the true size, color, and imprint.
☐	☒	**Yellow #5** (tartrazine) warning statement is properly displayed.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Latex** warning statement is properly displayed [21 CFR 801.437.].
☐	☒	**Gluten** statement is appropriately stated.
	PRODUCT DIFFERENTIATION:	
☐	☒	ANDA is the **same color** as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple **strengths are differentiated** by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from **related products**.
	STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:	
☐	☒	**Storage/dispensing** statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe **container closure**, cite source, and any issues in Reviewer Comments below.
	OVERALL ASSESSMENT:	
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Cycle 3:

The container labels and carton labeling were found acceptable in the C2 Labeling Review ; however, RLD container labels and carton labeling were revised in NDA 021135/S-037 (see Section 3.3 below). No new deficiencies are identified; thus, the ANDAs previously proposed container labels and carton labeling are satisfactory.

Cycle 4 Update 03/18/2025:

Related Products: Searched "iron sucrose" and "Sandoz" in CDEROne Nexus and did not identify any related products marketed by the Applicant.

Container closure: (b)(4)

(b)(4)

Cycle 5 Update 06/23/2025:

The Applicant addressed all of our Cycle 4 deficiencies as well as the 6/5/2025 DRL (Quality's recommendations) and 6/16/2025 IR. Acceptable.

Additional Note: Per internal meeting held on 07/01/2022 and 01/20/2023 between DLR, OPQ, OCC, ORP and OGDP, the decision was made to defer the review per 21 CFR 314.110. In addition, additional language was added in this review about existing citizen petition for Venofer [Docket ID: FDA 2005-P-0319]. Hence, the applicant revised (b)(4)
(b)(4)

Deficiency Comments:	
Deficiency # 1 Created in C4 Container Label	Decrease the prominence of the net quantity statement (i.e., 2.5 mL Single-Dose Vial, 5 mL Single-Dose Vial, 10 mL Single-Dose Vial) on all container labels so that it does not compete with the most critical information (e.g., established name, strength, route of administration, etc.), on the principal display panel (PDP). Refer to the Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors | FDA.
Response / Assessment:	**Applicant Response:** Sandoz has revised the container labels to decrease the prominence of the net quantity statement and changed the route of administration statement to title case. **Assessment:** Acceptable.
Deficiency # 2 Created in C4 Container Label	Revise the route of administration to title case (i.e., "For Intravenous Use Only") to be same as the RLD.
Response / Assessment:	**Applicant Response:** Sandoz has revised the container labels to decrease the prominence of the net quantity statement and changed the route of administration statement to title case. **Assessment:** Acceptable.

5.2.1 INJECTABLE PRODUCTS (C5)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Appropriate **package type term** was used (e.g. multiple-dose, single-dose, single-patient-use).
☐	☒	Product label states, "**Discard unused portion**" for single dose products.
☐	☒	IV, IM, or SC was spelled out.
☐	☒	There is **text on the cap/ferrule** overseal of this injectable product. If "Yes", does the text comply with the recommendations in USP General Chapter <7> Labeling.
☐	☒	The **cap color** is Green for the 50 mg vial and Purple for the 100 mg and 200 mg strength vial . ***NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.***

Reviewer Comments:

Deficiency Comments:

5.2.1.1 CONTAINER LABEL FOR PARENTERAL SOLUTIONS (C5)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	**Strength** expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP General Chapter <7> Labeling.
☐	☒	If volume is less than 1 mL, **strength per fraction of a milliliter** is the only expression of strength.
☐	☒	Quantity or proportion of all **inactive ingredients** listed on label as required under 1 CFR 201.100(b)(5)(iii).
☐	☒	Container label includes **instructions for reconstitution** if applicable.
☐	☒	**Aluminum content** is present on immediate container label (SVP, LVP, or PBP) and **warning** is present in the prescribing information.
Reviewer Comments: **Deficiency Comments:**		

5.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING (C5)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	**Unit-Dose Carton expression of strength** appropriately stated.
☐	☒	The answers to the Container Label questions are the same for the Carton Labeling. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Cycle 5 Update 06/23/2025:

The Applicant addressed all of our Cycle 4 deficiencies as well as the 6/5/2025 DRL (Quality's recommendations) and the 6/16/2025 IR. Acceptable.

Additional Note: Per internal meeting held on 07/01/2022 and 01/20/2023 between DLR, OPQ, OCC, ORP and OGDP, the decision was made to defer the review per 21 CFR 314.110. In addition, additional language was added in this review about existing citizen petition for Venofer [Docket ID: FDA 2005-P-0319]. Hence, the applicant revised (b)(4)

(b)(4)

Deficiency Comments:

Deficiency # 1 Created in C4 Carton Labeling Response / Assessment:	Side Panel: Add the word "Sterile" following the storage temperatures on all carton labeling to be same as the RLD. **Applicant Response:** Sandoz has revised the cartons to add the word "Sterile" following the storage temperatures, add "Sodium hydroxide may be added to adjust pH 10.5 to 11.1" to align with the RLD and changed the route of administration statement to title case. **Assessment:** Acceptable.
Deficiency # 2 Created in C4	Side Panel: Revise (b)(4) to "Sodium hydroxide may be added to adjust pH to 10.5 to 11.1." on all carton labeling to be same as the RLD.

Carton Labeling Response / Assessment:	**Applicant Response:** Sandoz has revised the cartons to add the word "Sterile" following the storage temperatures, add "Sodium hydroxide may be added to adjust pH 10.5 to 11.1" to align with the RLD and changed the route of administration statement to title case. **Assessment:** Acceptable.
Deficiency # 3 Created in C4 Carton Labeling Response / Assessment:	Refer to the comment under 1b. **Applicant Response:** Sandoz has revised the cartons to add the word "Sterile" following the storage temperatures, add "Sodium hydroxide may be added to adjust pH 10.5 to 11.1" to align with the RLD and changed the route of administration statement to title case. **Assessment:** Acceptable.

5.4 PRESCRIBING INFORMATION (C5)

Reviewer Assessment:

Deficiency	No Deficiency	
		HIGHLIGHTS:
☐	☒	**Contact information** for applicant and FDA are listed correctly.
☐	☒	**Revision date** appears at the end of HIGHLIGHTS section (PLR) or end of prescribing information (non-PLR).
		DESCRIPTION/INACTIVE INGREDIENTS:
		Appropriate **warning/precaution** statements for inactive ingredients are present (21 CFR 201) Check only if applicable:
☐	☒	☐ Sulfite (21 CFR 201.22) ☐ Yellow #5 (Tartrazine) (21 CFR 201.20) ☐ Phenylalanine/aspartame (21 CFR 201.21) ☐ Latex (21 CFR 801.437).
☐	☒	**Sterile** product statement [21 CFR 201.57(c)(12)(i)(D)].
☐	☒	☐ **Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	☐ **Gluten** statement is appropriately stated.
☐	☒	**Dosage form, pharmacologic/therapeutic class, and route** of administration properly listed [21 CFR 201.57(c)(12)(i)(B)] and[21 CFR 201.57(c)(12)(i)(E)].
		HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:
☐	☒	All **submitted labels** and labeling are consistent with the HOW SUPPLIED section.
☐	☒	**Physical description** (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	**NDC** numbers are present.
☐	☒	Drug product is the **same color** as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	**Storage or dispensing** statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**"Discard unused portion"** for single-dose products.

Deficiency	No Deficiency	
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
	REGULATORY/OVERALL ASSESSMENT:	
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the **Antiretroviral Pregnancy Registry** (APR) upon full approval.
☐	☒	**Pregnancy registry** information is appropriately included/excluded as required for the RLD.
☐	☒	**Patent/exclusivity** carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Dosage form/strength** carve out (RLD combined labeling): justification for retaining information for safety/efficacy.
☐	☒	Prescribing information meets **formatting requirements** [21 CFR 201.57 (PLR) or 21 CFR 201.80 (non-PLR)].
☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Cycle 5 Update 06/23/2025:

The Applicant addressed all of our Cycle 4 deficiencies as well as the 6/5/2025 DRL (Quality's recommendations) and 6/16/2025 IR. Acceptable.

Additional Note #1: Per internal meeting held on 07/01/2022 and 01/20/2023 between DLR, OPQ, OCC, ORP and OGDP, the decision was made to defer the review per 21 CFR 314.110. In addition, additional language was added in this review about existing citizen petition for Venofer [Docket ID: FDA 2005-P-0319]. Hence, the applicant revised

(b)(4)

Additional Note #2: In reviewing and evaluating this application, DLR has determined the labeling differences proposed by the Applicant, with respect to the listing of sodium chloride as a tonicity agent, fall within the "different manufacturers" exception to the same labeling requirement.

Section 505(j)(2)(A)(v) of the FD&C Act requires that an ANDA contain "information to show that the labeling proposed for the new [generic] drug is the same as the labeling approved for the listed drug...except for changes required because of differences approved under a petition filed under [section 505(j)(2)(C) of the FD&C Act] or because the new [generic] drug and the listed drug are produced or distributed by different manufacturers." A parallel provision appears in section 505(j)(4)(G) of the FD&C Act.

Although the requirement set forth in sections 505(j)(2)(A)(v) and 505(j)(4)(G) of the FD&C Act is known as the "same labeling" requirement, it does not require that a generic drug's labeling be identical to that of the listed drug it references in every respect. Section 314.94(a)(8)(iv) sets forth examples of permissible differences in labeling that may result because the generic drug product and RLD are produced or distributed by different manufacturers. Permissible differences include, but are not limited to, the following:
...[D]ifferences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the Federal Food, Drug, and Cosmetic Act.

Therefore, from a labeling perspective, the resulting labeling differences, are permitted exceptions to the same labeling requirement under section 505(j)(2)(A)(v) of the FD&C Act and 21 CFR 314.94(a)(8)(iv), which allow for labeling differences attributable to the products being produced or distributed by different manufacturers.

Deficiency Comments:	
Deficiency # 1 Created in C4 Prescribing Information	HOW SUPPLIED/ STORAGE AND HANDLING: Add your product description (e.g., shape, color, scoring, coating, and imprint code) to be in accordance with the information in your submission, as required per 21 CFR 201.57(c)(17).
Response / Assessment:	**Applicant Response:** Sandoz has revised the HOW SUPPLIED/STORAGE AND HANDLING Section of the prescribing information to add "USP," the product description and "Discard unused portion." **Assessment:** Acceptable.
Deficiency # 2 Created in C4 Prescribing Information	HOW SUPPLIED/STORAGE AND HANDLING: Add "Discard unused portion" to this section as the proposed product is for a single-dose container. Refer to the Guidance for Industry - Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Container for Human Use.
Response / Assessment:	**Applicant Response:** Sandoz has revised the HOW SUPPLIED/STORAGE AND HANDLING Section of the prescribing information to add "USP," the product description and "Discard unused portion." **Assessment:** Acceptable.

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C5)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☒	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:

Comments from C2 Labeling Review

"Questions to the chemist:
Did the firm submit **studies that support** the following found in the Prescribing Information?

Syringe Stability: Iron sucrose injection, when diluted with 0.9% NaCl at concentrations ranging from 2 mg to 10 mg of elemental iron per mL, or undiluted (20 mg elemental iron per mL) and stored in a plastic syringe, was found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C) and under refrigeration (4°C ± 2°C).

Intravenous Admixture Stability: Iron sucrose injection, when added to intravenous infusion bags (PVC or non-PVC) containing 0.9% NaCl at concentrations ranging from 1 mg to 2 mg of elemental iron per mL, has been found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C)."

- **RESPONSE**: "The firm did provide compatibility study data. Please see my assessment of the study on page 52-53 of my DP quality review. The compatibility data is adequate."

Deficiency Comments:

Cameron Clark

Digitally signed by Cameron Clark
Date: 6/27/2025 09:33:36AM
GUID: 5a4fa1f0001c26bc28df0e20df234537

Ellen Hwang

Digitally signed by Ellen Hwang
Date: 6/27/2025 09:53:15AM
GUID: 5256bdc00002af3bc3fa942a9512a891

Labeling Review
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	03/17/2025, 05/19/2025
ANDA Number(s)	212340
Review Number	4 Addendum (b)(4) (b)(4)
Applicant Name	Sandoz Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Iron Sucrose Injection USP, 50 mg Elemental Iron/2.5 mL (20 mg/mL), 100 mg Elemental Iron/5 mL (20 mg/mL), 200 mg Elemental Iron/10 mL (20 mg/mL) (Single-Dose Vials)
Proposed Proprietary Name	N/A
Submission Received Date	August 18, 2023, April 4, 2024, August 5, 2024
Primary Labeling Reviewer	Cameron Clark
Secondary Labeling Reviewer	Ellen Hwang

Review Conclusion

☐ Acceptable - No Comments
☐ Acceptable - Include Post Approval Comments
☒ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant
☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List	☒ Yes	☐ No
Acceptable For Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No

TABLE OF CONTENTS

1 LABELING COMMENTS (C4 ADDENDUM)

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C4 ADDENDUM)

1. GENERAL COMMENTS

On April 15, 2016, Foley Hoag LLP submitted a Citizen Petition (Docket No. FDA-2016-P-1163) requesting, among other things, that FDA recognize that Velphoro (new drug application (NDA) 205109) is eligible for 5-year new chemical entity (NCE) exclusivity under 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (Velphoro Citizen Petition). On May 26, 2021, FDA published a response to the Velphoro Citizen Petition in which we denied the request, among other things, and determined that Velphoro's active moiety and active ingredient are ferric oxyhydroxide.

Following publication of the Velphoro Citizen Petition response, the Agency accordingly issued a revised draft product-specific guidance (PSG), updated the Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book) and Drugs@FDA. Please be advised that the agency intends to consider additional regulatory actions and/or policy changes to address certain issues implicated by this petition response.

Additionally, on August 3, 2021, Vifor (International) Inc., Switzerland (Vifor) submitted a Citizen Petition and Petition for Stay (Docket No. FDA-2021-P-0893) (Vifor Petition) requesting the Agency reverse certain actions announced in its Velphoro Citizen Petition response. The issues raised by the Vifor petition are under review by the Agency, and FDA has not made a final decision on these issues. On July 1, 2024, the Agency published a memorandum stating that the Center for Drug Evaluation and Research (CDER) "is reevaluating its determination that the active ingredient of the iron products subject to the May 26, 2021, Citizen Petition response is ferric oxyhydroxide." The memorandum also stated that during the reevaluation period, "CDER is accepting the active ingredient names as approved prior to the May 26, 2021, Citizen Petition response for all iron products subject to the May 26, 2021, Citizen Petition response..." (See Docket Nos FDA-2016-P-1163 and FDA-2021-P-0893, available at regulations.gov.).

Also note that Sonnenschein, Nath & Rosenthal LLP submitted a Citizen Petition (Docket No. FDA-2005-P-0319) (Venofer Citizen Petition) requesting, among other things, that the FDA adopt and apply certain requirements to ensure "the even-handed application of the requirements of Section 505 of the [FD&C Act] and the safety and efficacy of any generic version or pharmaceutical equivalent" of Venofer (Venofer Citizen Petition, at 2). The issues raised by that petition are under review by the Agency, and the FDA has not made a final decision on these issues.

2. CONTAINER LABEL

a. Decrease the prominence of the net quantity statement (i.e., 2.5 mL Single-Dose Vial, 5 mL Single-Dose Vial, 10 mL Single-Dose Vial) on all container labels so that it does not compete with the most critical information (e.g., established name, strength, route of administration, etc.), on the principal display panel (PDP). Refer to the Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors | FDA.

b. Revise the route of administration to title case (i.e., "For Intravenous Use Only") to be same as the RLD.

3. CARTON LABELING
   a. Side Panel: Add the word "Sterile" following the storage temperatures on all carton labeling to be same as the RLD.
   b. Side Panel: Revise (b)(4) to "Sodium hydroxide may be added to adjust pH to 10.5 to 11.1." on all carton labeling to be same as the RLD.
   c. Refer to the comment under 1b.

4. PRESCRIBING INFORMATION
   a. HOW SUPPLIED/STORAGE AND HANDLING: Add the "USP" descriptor to the HOW SUPPLIED/STORAGE AND HANDLING section.
   b. HOW SUPPLIED/ STORAGE AND HANDLING: Add your product description (e.g., shape, color, scoring, coating, and imprint code) to be in accordance with the information in your submission, as required per 21 CFR 201.57(c)(17).
   c. HOW SUPPLIED/STORAGE AND HANDLING: Add "Discard unused portion" to this section as the proposed product is for a single-dose container. Refer to the Guidance for Industry - Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Container for Human Use.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with Please enter text labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C4 ADDENDUM)

1.3 POST-APPROVAL REVISIONS (C4 ADDENDUM)

These comments will be addressed post approval (in the first labeling supplement review).

2 INSTRUCTIONS FOR ASSESSMENT (C4 ADDENDUM)

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

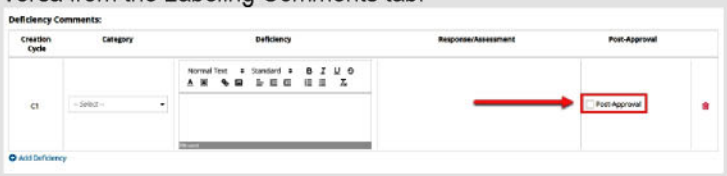
If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:
Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the DLR Standardized Comments SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.



3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C4 ADDENDUM)

Table 1: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	50 mg/2.5 mL single dose vials 100 mg/5 mL single dose vials 200 mg/10 mL single dose vials	10/31/2019	Revise
Blister	N/A	N/A		
Carton	Final	50 mg/2.5 mL single dose vials: cartons of 10s and 25s 100 mg/5 mL single dose vials: cartons of 10s and 25s 200 mg/10 mL single dose vials: cartons of 5s and 10s	10/31/2019	Revise

Table 2: Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	Revised: 08/2024	08/05/2024	Revise
Medication Guide	N/A	N/A		

Table 2: Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Patient Information	N/A	N/A		
Instructions for Use	N/A	N/A		
SPL Data Elements				

4 LABELING REVIEW INFORMATION(C4 ADDENDUM)

4.1 REGULATORY INFORMATION (C4 ADDENDUM)

Yes	No	
☐	☒	Are there any applicable issues in DLR's SharePoint Drug Facts ?
☒	☐	Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint?

(b)(2)

Yes	No	
		(b)(2)

4.2 MODEL PRESCRIBING INFORMATION (C4 ADDENDUM)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): NDA021135 / S-038

Supplement Approval Date: 08/01/2024

Proprietary Name: Venofer Injection

Established Name: Iron Sucrose Injection, USP

Description of Supplement:

Please refer to your supplemental new drug application (sNDA) dated and received June 10, 2022, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Venofer (iron sucrose) injection.

We also refer to our letter dated May 11, 2022, requesting you submit draft labeling for your Prescribing Information in accordance with the requests below:

In Section 6.2 add the following information (additions are shown as underlined text and deletions are shown as strikethroughs):

- ~~Cardiac disorders: bradycardia~~
- ~~Vascular disorders: shock~~
- Cardiovascular System: bradycardia, shock, acute myocardial ischemia with or without myocardial infarction or with in-stent thrombosis in the context of a hypersensitivity reaction.

This "Changes Being Effected" sNDA provides for these requested changes.

Link: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8075ccca

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

☒ **OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):**

S-040 and S-041 are CMC supplements approved after the model labeling that did not have an impact on labeling.

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is **up-to-date** with the RLD/Model labeling.

Reviewer Comments:

Internal

An internal meeting was held on 07/16/2021 between DLR, OPQ, and OGDP to discuss the implication of Velphoro CP response (Docket No. FDA-2016-P-1163; 5/26/2021) which clarified that the active ingredient for the drug products containing ferric oxyhydroxide (iron(III) oxyhydroxide) and carbohydrate sugars is

"Ferric Oxyhydroxide". This determination has so far changed the identity of the active ingredient for the iron carbohydrate drug products in the Orange Book and Drugs@FDA, and therefore the identity of the active ingredient for Venofer has also changed from "Iron Sucrose" to "Ferric Oxyhydroxide" in Orange Book and Drugs@FDA. With further such updates anticipated in the USP and RLD labeling, there will be, among other changes, labeling implication such as with the presentation of the established name, as the generic drug products would need to be consistent with the USP designation and RLD labeling. Therefore, the Agency has determined to defer this review per 21 CFR 314.110 and issue the following comments to the applicant.

Cycle 4 Update 03/18/2025:
ANDA labeling is modeled after the RLD's S-038 labeling

The following deficiency was included in the Cycle 3 addendum review:
GENERAL COMMENTS: We acknowledge receipt of your amendment received on December 28, 2020, which was deferred per 21 CFR 314.110 and not reviewed for this action. You may incorporate applicable sections of the deferred amendment by specific reference as part of your response to the deficiencies cited in this letter.

On 04/17/2023, the application received a complete response letter (CRL) due to drug substance, drug product, and bioequivalence deficiencies. Our labeling deficiency was also included in the CRL. On 08/18/2023, the Applicant provided their complete response to the deficiencies included in the CRL. On 04/04/2024 the Applicant submitted revised labeling to be same as the RLD updated labeling. Furthermore, on 08/05/2024, the Applicant submitted revised labeling

(b)(4)

Cycle 4 Addendum Update 05/19/2025:
On 05/19/2025, OGDP provided the following language to incorporate to be conveyed to the Applicant. We have included the language as a general comment for the Applicant below.

On April 15, 2016, Foley Hoag LLP submitted a Citizen Petition (Docket No. FDA-2016-P-1163) requesting, among other things, that FDA recognize that Velphoro (new drug application (NDA) 205109) is eligible for 5-year new chemical entity (NCE) exclusivity under 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (Velphoro Citizen Petition). On May 26, 2021, FDA published a response to the Velphoro Citizen Petition in which we denied the request, among other things, and determined that Velphoro's active moiety and active ingredient are ferric oxyhydroxide.

Following publication of the Velphoro Citizen Petition response, the Agency accordingly issued a revised draft product-specific guidance (PSG), updated the Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book) and Drugs@FDA. Please be advised that the agency intends to consider additional regulatory actions and/or policy changes to address certain issues implicated by this petition response.

Additionally, on August 3, 2021, Vifor (International) Inc., Switzerland (Vifor) submitted a Citizen Petition and Petition for Stay (Docket No. FDA-2021-P-0893) (Vifor Petition) requesting the Agency reverse certain actions announced in its Velphoro Citizen Petition response. The issues raised by the Vifor petition are under review by the Agency, and FDA has not made a final decision on these issues. On July 1, 2024, the Agency published a memorandum stating that the Center for Drug Evaluation and Research (CDER) "is reevaluating its determination that the active ingredient of the iron products subject to the May 26, 2021, Citizen Petition response is ferric oxyhydroxide." The memorandum also stated that during the reevaluation

period, "CDER is accepting the active ingredient names as approved prior to the May 26, 2021, Citizen Petition response for all iron products subject to the May 26, 2021, Citizen Petition response..." (See Docket Nos FDA-2016-P-1163 and FDA-2021-P-0893, available at regulations.gov.).

Also note that Sonnenschein, Nath & Rosenthal LLP submitted a Citizen Petition (Docket No. FDA-2005-P-0319) (Venofer Citizen Petition) requesting, among other things, that the FDA adopt and apply certain requirements to ensure "the even-handed application of the requirements of Section 505 of the [FD&C Act] and the safety and efficacy of any generic version or pharmaceutical equivalent" of Venofer (Venofer Citizen Petition, at 2). The issues raised by that petition are under review by the Agency, and the FDA has not made a final decision on these issues.

Deficiency Comments:

Deficiency # 1 Created in C4 (Addendum) General Comments	On April 15, 2016, Foley Hoag LLP submitted a Citizen Petition (Docket No. FDA-2016-P-1163) requesting, among other things, that FDA recognize that Velphoro (new drug application (NDA) 205109) is eligible for 5-year new chemical entity (NCE) exclusivity under 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (Velphoro Citizen Petition). On May 26, 2021, FDA published a response to the Velphoro Citizen Petition in which we denied the request, among other things, and determined that Velphoro's active moiety and active ingredient are ferric oxyhydroxide. Following publication of the Velphoro Citizen Petition response, the Agency accordingly issued a revised draft product-specific guidance (PSG), updated the Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book) and Drugs@FDA. Please be advised that the agency intends to consider additional regulatory actions and/or policy changes to address certain issues implicated by this petition response. Additionally, on August 3, 2021, Vifor (International) Inc., Switzerland (Vifor) submitted a Citizen Petition and Petition for Stay (Docket No. FDA-2021-P-0893) (Vifor Petition) requesting the Agency reverse certain actions announced in its Velphoro Citizen Petition response. The issues raised by the Vifor petition are under review by the Agency, and FDA has not made a final decision on these issues. On July 1, 2024, the Agency published a memorandum stating that the Center for Drug Evaluation and Research (CDER) "is reevaluating its determination that the active ingredient of the iron products subject to the May 26, 2021, Citizen Petition response is ferric oxyhydroxide." The memorandum also stated that during the reevaluation period, "CDER is accepting the active ingredient names as approved prior to the May 26, 2021, Citizen Petition response for all iron products subject to the May 26, 2021, Citizen Petition response..." (See Docket Nos FDA-2016-P-1163 and FDA-2021-P-0893, available at regulations.gov.). Also note that Sonnenschein, Nath & Rosenthal LLP submitted a Citizen Petition (Docket No. FDA-2005-P-0319) (Venofer Citizen Petition) requesting, among other things, that the FDA adopt and apply certain requirements to ensure "the even-handed application of the requirements of Section 505 of the [FD&C Act] and the safety and efficacy of any

Response / Assessment:	generic version or pharmaceutical equivalent" of Venofer (Venofer Citizen Petition, at 2). The issues raised by that petition are under review by the Agency, and the FDA has not made a final decision on these issues.

4.3 PATENTS AND EXCLUSIVITIES (C4 ADDENDUM)

The Orange Book was searched on 05/19/2025

Table 4 provides Orange Book patents for the Model Labeling (NDA021135) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
	N/A						

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

Strengths	Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
	N/A					

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has **expired** and the applicant needs to revise labeling.
Reviewer Comments: **Deficiency Comments:**		

4.4 UNITED STATES PHARMACOPEIA (USP) (C4 ADDENDUM)

The USP was searched on 03/17/2025

Table 6: USP

	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
Currently Official	Yes		Iron Sucrose Injection	ADDITIONAL REQUIREMENTS Change to read:

Table 6: USP				
	YES or NO	**Date**	**Monograph Title (N/A if no monograph)**	**Packaging and Storage/Labeling Statements (N/A if no monograph)**
				•Packaging and Storage: Preserve in single-dose containers▲ , preferably▲ (RB 1-Apr-2023)of Type I glass. Store at controlled room temperature. Do not freeze. •Labeling: Label it to indicate that it is for intravenous use only, and that when administered by intravenous infusion, the Injection must be diluted with 0.9% Sodium Chloride Injection to a concentration of 1.0–2.0 mg/mL of elemental iron. Label it also to state the total osmolarity of the solution expressed in mOsmol/L.
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

Deficiency	**No Deficiency**	
☐	☒	**Established name** is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary **name is different from USP** established name.
☒	☐	**USP descriptor** is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	**DISSOLUTION**: The applicant's dissolution statement is appropriate.
☐	☒	**ORGANIC IMPURITIES**: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	**ASSAY**: Drug product meets USP acceptance criteria for assay.
Reviewer Comments: **Deficiency Comments:**		

Deficiency # 1 Created in C4 Prescribing Information Response / Assessment:	HOW SUPPLIED/STORAGE AND HANDLING: Add the "USP" descriptor to the HOW SUPPLIED/STORAGE AND HANDLING section.

4.5 MODEL CONTAINER LABELS (C4 ADDENDUM)

Model container/carton/blister labels (Source: carton labeling: ANRPT-21 (submitted on 12/16/2021) and ANRPT-24 (submitted 12/18/2024); container label: ANRPT-20 (submitted on 12/17/2020) **)**

5 ASSESSMENT OF ANDA LABELING AND LABELS (C4 ADDENDUM)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C4 ADDENDUM)

5.1.1 DRUG PRODUCT REVIEW (C4 ADDENDUM)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review pending

Comments from C2 Labeling Review
"CHEMISTRY is INADEQAUTE-MAJOR as of this labeling review cycle dated 4/14/2020."

C3 Labeling Review Updates
DP Review (Reference #44536490) is pending. Per the prescreen checklist, "List of Deficiencies: NA."

5.1.2 DESCRIPTION (C4 ADDENDUM)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	Each mL contains 20 mg elemental iron as iron sucrose in water for injection. Venofer is available in 5 mL single-dose vials (100 mg elemental iron per 5 mL). The drug product contains approximately 30% sucrose w/v (300 mg/mL). Sodium hydroxide may be added to adjust pH to 10.5 to 11.1. The product contains no preservatives. The osmolarity of the injection is 1,250 mOsmol/L.
Previous ANDA Labeling	(b)(4)
Current ANDA Labeling	

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C4 ADDENDUM)

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	16.1 How Supplied

Table 8: Comparison of Model Labeling to ANDA Labeling	
	Venofer is supplied sterile in 5 mL single-dose vials. Each 5 mL vial contains 100 mg elemental iron (20 mg/mL). NDC-0517-2340-99 100 mg/5 mL Single-Dose Vial Packages of 10 16.2 Stability and Storage Contains no preservatives. Store in original carton at 20° to 25°C (68° to 77° F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not freeze. Syringe Stability: Venofer, when diluted with 0.9% NaCl at concentrations ranging from 2 mg to 10 mg of elemental iron per mL, or undiluted (20 mg elemental iron per mL) and stored in a plastic syringe, was found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C) and under refrigeration (4°C ± 2°C). Intravenous Admixture Stability: Venofer, when added to intravenous infusion bags (PVC or non-PVC) containing 0.9% NaCl at concentrations ranging from 1 mg to 2 mg of elemental iron per mL, has been found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C). Do not dilute to concentrations below 1 mg/mL. Do not mix Venofer with other medications or add to parenteral nutrition solutions for intravenous infusion. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to infusion.
Previous ANDA Labeling	(b)(4)

Table 8: Comparison of Model Labeling to ANDA Labeling	
Current ANDA Labeling	(b)(4)

Table 8: Comparison of Model Labeling to ANDA Labeling	
	(b)(4)

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C4 ADDENDUM)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Previous ANDA Labeling	
Name and Address on ANDA Prescribing Information	(b)(4)
Current ANDA Labeling	
Name and Address on ANDA Prescribing Information	Manufactured by Rafarm S.A. for Sandoz Inc., Princeton, NJ 08540 **Reviewer Assessment:** (b)(4) Acceptable.

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements			
Manufactured by	**Manufactured for**	**Distributed by**	**Distributed for**

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C4 ADDENDUM)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the **too small exemption** [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
		ESTABLISHED/PROPRIETARY NAME and STRENGTH:
☐	☒	**Tall Man** lettering complies with recommendations found on FDA webpage.
☒	☐	Established/proprietary **name and strength are the most prominent** information on the Principal Display Panel.
☐	☒	No **intervening text**(written, printed, or graphic matter) between established name and strength.
		THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:
☐	☒	**Net quantity** statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Dosage** statement.
☐	☒	**NDC number:** prominence, linear bar code, and its orientation.
☐	☒	**Expiration date and lot number** (or placeholder).
☐	☒	**Equivalency statement** (product strength).
☐	☒	**Medication Guide** Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol.
☐	☒	**Image of drug product** represents the true size, color, and imprint.
☐	☒	**Yellow #5** (tartrazine) warning statement is properly displayed.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Latex** warning statement is properly displayed [21 CFR 801.437.].

Deficiency	No Deficiency	
☐	☒	**Gluten** statement is appropriately stated.
	PRODUCT DIFFERENTIATION:	
☐	☒	ANDA is the **same color** as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple **strengths are differentiated** by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from **related products**.
	STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:	
☐	☒	**Storage/dispensing** statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe **container closure**, cite source, and any issues in Reviewer Comments below.
	OVERALL ASSESSMENT:	
☒	☐	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Cycle 3:

The container labels and carton labeling were found acceptable in the C2 Labeling Review ; however, RLD container labels and carton labeling were revised in NDA 021135/S-037 (see Section 3.3 below). No new deficiencies are identified; thus, the ANDAs previously proposed container labels and carton labeling are satisfactory.

Cycle 4 Update 03/18/2025:

Related Products: Searched "iron sucrose" and "Sandoz" in CDEROne Nexus and did not identify any related products marketed by the Applicant.

Container closure: (b)(4)

(b)(4)

Deficiency Comments:

Deficiency # 1 Created in C4 Container Label Response / Assessment:	Decrease the prominence of the net quantity statement (i.e., 2.5 mL Single-Dose Vial, 5 mL Single-Dose Vial, 10 mL Single-Dose Vial) on all container labels so that it does not compete with the most critical information (e.g., established name, strength, route of administration, etc.), on the principal display panel (PDP). Refer to the Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors | FDA.
Deficiency # 2 Created in C4 Container Label Response / Assessment:	Revise the route of administration to title case (i.e., "For Intravenous Use Only") to be same as the RLD.

5.2.1 INJECTABLE PRODUCTS (C4 ADDENDUM)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Appropriate **package type term** was used (e.g. multiple-dose, single-dose, single-patient-use).
☐	☒	Product label states, "**Discard unused portion**" for single dose products.
☐	☒	IV, IM, or SC was spelled out.
☐	☒	There is **text on the cap/ferrule** overseal of this injectable product. If "Yes", does the text comply with the recommendations in USP General Chapter <7> Labeling.
☐	☒	The **cap color** is Green for the 50 mg vial and Purple for the 100 mg and 200 mg strength vial . ***NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.***
Reviewer Comments: **Deficiency Comments:**		

5.2.1.1 CONTAINER LABEL FOR PARENTERAL SOLUTIONS (C4 ADDENDUM)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	**Strength** expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP General Chapter <7> Labeling.
☐	☒	If volume is less than 1 mL, **strength per fraction of a milliliter** is the only expression of strength.
☐	☒	Quantity or proportion of all **inactive ingredients** listed on label as required under 1 CFR 201.100(b)(5)(iii).
☐	☒	Container label includes **instructions for reconstitution** if applicable.
☐	☒	**Aluminum content** is present on immediate container label (SVP, LVP, or PBP) and **warning** is present in the prescribing information.
Reviewer Comments: **Deficiency Comments:**		

5.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING (C4 ADDENDUM)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	**Unit-Dose Carton expression of strength** appropriately stated.
☒	☐	The answers to the Container Label questions are the same for the Carton Labeling. Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments: **Deficiency Comments:** Deficiency # 1 Created in C4 Carton Labeling Response / Assessment:		Side Panel: Add the word "Sterile" following the storage temperatures on all carton labeling to be same as the RLD.

Deficiency # 2 Created in C4 Carton Labeling Response / Assessment:	Side Panel: Revise [redacted] to "Sodium hydroxide may be added to adjust pH to 10.5 to 11.1." on all carton labeling to be same as the RLD.
Deficiency # 3 Created in C4 Carton Labeling Response / Assessment:	Refer to the comment under 1b.

5.4 PRESCRIBING INFORMATION (C4 ADDENDUM)

Reviewer Assessment:

Deficiency	No Deficiency	
	HIGHLIGHTS:	
☐	☒	**Contact information** for applicant and FDA are listed correctly.
☐	☒	**Revision date** appears at the end of HIGHLIGHTS section (PLR) or end of prescribing information (non-PLR).
	DESCRIPTION/INACTIVE INGREDIENTS:	
	Appropriate **warning/precaution** statements for inactive ingredients are present (21 CFR 201) Check only if applicable:	
☐	☒	☐ Sulfite (21 CFR 201.22) ☐ Yellow #5 (Tartrazine) (21 CFR 201.20) ☐ Phenylalanine/aspartame (21 CFR 201.21) ☐ Latex (21 CFR 801.437).
☐	☒	**Sterile** product statement [21 CFR 201.57(c)(12)(i)(D)].
☐	☒	☐ **Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	☐ **Gluten** statement is appropriately stated.
☐	☒	**Dosage form, pharmacologic/therapeutic class, and route** of administration properly listed [21 CFR 201.57(c)(12)(i)(B)] and[21 CFR 201.57(c)(12)(i)(E)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	All **submitted labels** and labeling are consistent with the HOW SUPPLIED section.
☒	☐	**Physical description** (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	**NDC** numbers are present.
☐	☒	Drug product is the **same color** as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	**Storage or dispensing** statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☒	☐	**"Discard unused portion"** for single-dose products.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
	REGULATORY/OVERALL ASSESSMENT:	
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the **Antiretroviral Pregnancy Registry** (APR) upon full approval.
☐	☒	**Pregnancy registry** information is appropriately included/excluded as required for the RLD.

Deficiency	No Deficiency	
☐	☒	**Patent/exclusivity** carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Dosage form/strength** carve out (RLD combined labeling): justification for retaining information for safety/efficacy.
☐	☒	Prescribing information meets **formatting requirements** [21 CFR 201.57 (PLR) or 21 CFR 201.80 (non-PLR)].
☒	☐	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Deficiency Comments:

Deficiency # 1 Created in C4 Prescribing Information Response / Assessment:	HOW SUPPLIED/ STORAGE AND HANDLING: Add your product description (e.g., shape, color, scoring, coating, and imprint code) to be in accordance with the information in your submission, as required per 21 CFR 201.57(c)(17).
Deficiency # 2 Created in C4 Prescribing Information Response / Assessment:	HOW SUPPLIED/STORAGE AND HANDLING: Add "Discard unused portion" to this section as the proposed product is for a single-dose container. Refer to the Guidance for Industry - Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Container for Human Use.

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C4 ADDENDUM)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☒	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:

Comments from C2 Labeling Review

"Questions to the chemist:
Did the firm submit **studies that support** the following found in the Prescribing Information?

Syringe Stability: Iron sucrose injection, when diluted with 0.9% NaCl at concentrations ranging from 2 mg to 10 mg of elemental iron per mL, or undiluted (20 mg elemental iron per mL) and stored in a plastic syringe, was found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C) and under refrigeration (4°C ± 2°C).

Intravenous Admixture Stability: Iron sucrose injection, when added to intravenous infusion bags (PVC or non-PVC) containing 0.9% NaCl at concentrations ranging from 1 mg to 2 mg of elemental iron per mL, has been found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C)."

- **RESPONSE**: "The firm did provide compatibility study data. Please see my assessment of the study on page 52-53 of my DP quality review. The compatibility data is adequate."

Deficiency Comments:

Cameron Clark

Digitally signed by Cameron Clark
Date: 5/22/2025 02:33:07PM
GUID: 5a4fa1f0001c26bc28df0e20df234537

Ellen Hwang

Digitally signed by Ellen Hwang
Date: 5/22/2025 04:16:03PM
GUID: 5256bdc00002af3bc3fa942a9512a891

Labeling Review

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	March 17, 2025
ANDA Number(s)	212340
Review Number	4
Applicant Name	Sandoz Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Iron Sucrose Injection USP, 50 mg Elemental Iron/2.5 mL (20 mg/mL), 100 mg Elemental Iron/5 mL (20 mg/mL), 200 mg Elemental Iron/10 mL (20 mg/mL) (Single-Dose Vials)
Proposed Proprietary Name	N/A
Submission Received Date	August 18, 2023, April 4, 2024, August 5, 2024
Primary Labeling Reviewer	Cameron Clark
Secondary Labeling Reviewer	Ellen Hwang

Review Conclusion

☐ Acceptable - No Comments
☐ Acceptable - Include Post Approval Comments
☒ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant
☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List	☒ Yes	☐ No
Acceptable For Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No

TABLE OF CONTENTS

1 LABELING COMMENTS (C4)

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C4)

The following comments have been identified by the Division of Labeling Review (DLR) based on your submission(s) on August 18, 2023, April 4, 2024, August 5, 2024. Prior to final approval, the proposed labeling should be clear and precise (grammar, spelling, and formatting) for end users, and accurately reflect the Reference Listed Drug (RLD) information to comply with FDA policies, laws, regulations (i.e., 21 CFR 314.94(a)(8)), official compendia, and relevant guidance.

1. CONTAINER LABEL
    a. Decrease the prominence of the net quantity statement (i.e., 2.5 mL Single-Dose Vial, 5 mL Single-Dose Vial, 10 mL Single-Dose Vial) on all container labels so that it does not compete with the most critical information (e.g., established name, strength, route of administration, etc.), on the principal display panel (PDP). Refer to the Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors | FDA.
    b. Revise the route of administration to title case (i.e., "For Intravenous Use Only") to be same as the RLD.

2. CARTON LABELING
    a. Side Panel: Add the word "Sterile" following the storage temperatures on all carton labeling to be same as the RLD.
    b. Side Panel: Revise [(b)(4)]" to "Sodium hydroxide may be added to adjust pH to 10.5 to 11.1." on all carton labeling to be same as the RLD.
    c. Refer to the comment under 1b.

3. PRESCRIBING INFORMATION
    a. HOW SUPPLIED/STORAGE AND HANDLING: Add the "USP" descriptor to the HOW SUPPLIED/STORAGE AND HANDLING section.
    b. HOW SUPPLIED/ STORAGE AND HANDLING: Add your product description (e.g., shape, color, scoring, coating, and imprint code) to be in accordance with the information in your submission, as required per 21 CFR 201.57(c)(17).
    c. HOW SUPPLIED/STORAGE AND HANDLING: Add “Discard unused portion” to this section as the proposed product is for a single-dose container. Refer to the Guidance for Industry - Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Container for Human Use.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary

revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C4)

1.3 POST-APPROVAL REVISIONS (C4)

These comments will be addressed post approval (in the first labeling supplement review).

2 INSTRUCTIONS FOR ASSESSMENT (C4)

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:
Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the DLR Standardized Comments SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C4)

Table 1: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	50 mg/2.5 mL single dose vials 100 mg/5 mL single dose vials 200 mg/10 mL single dose vials	10/31/2019	Revise
Blister	N/A	N/A		
Carton	Final	50 mg/2.5 mL single dose vials: cartons of 10s and 25s 100 mg/5 mL single dose vials: cartons of 10s and 25s 200 mg/10 mL single dose vials: cartons of 5s and 10s	10/31/2019	Revise

Table 2: Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	Revised: 08/2024	08/05/2024	Revise
Medication Guide	N/A	N/A		
Patient Information	N/A	N/A		
Instructions for Use	N/A	N/A		
SPL Data Elements				

4 LABELING REVIEW INFORMATION(C4)

4.1 REGULATORY INFORMATION (C4)

Yes	No	
☐	☒	Are there any applicable issues in **DLR's SharePoint Drug Facts** ?
☒	☐	(b)(2)

Yes	No	
		(b)(2)

4.2 MODEL PRESCRIBING INFORMATION (C4)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): NDA021135 / S-038

Supplement Approval Date: 08/01/2024

Proprietary Name: Venofer Injection

Established Name: Iron Sucrose Injection, USP

Description of Supplement:

Please refer to your supplemental new drug application (sNDA) dated and received June 10, 2022, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Venofer (iron sucrose) injection.

We also refer to our letter dated May 11, 2022, requesting you submit draft labeling for your Prescribing Information in accordance with the requests below:

In Section 6.2 add the following information (additions are shown as underlined text and deletions are shown as strikethroughs):

- ~~Cardiac disorders: bradycardia~~
- ~~Vascular disorders: shock~~
- Cardiovascular System: bradycardia, shock, acute myocardial ischemia with or without myocardial infarction or with in-stent thrombosis in the context of a hypersensitivity reaction.

This "Changes Being Effected" sNDA provides for these requested changes.

Link: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8075ccca

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)
☐ MOST RECENTLY APPROVED ANDA MODEL LABELING
☒ OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out): S-040 and S-041 are CMC supplement approved after the model labeling that did not have an impact on labeling.

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is **up-to-date** with the RLD/Model labeling.

Reviewer Comments:

Cycle 3

Internal

An internal meeting was held on 07/16/2021 between DLR, OPQ, and OGDP to discuss the implication of Velphoro CP response (Docket No. FDA-2016-P-1163; 5/26/2021) which clarified that the active ingredient for the drug products containing ferric oxyhydroxide (iron(III) oxyhydroxide) and carbohydrate sugars is "Ferric Oxyhydroxide". This determination has so far changed the identity of the active ingredient for the iron carbohydrate drug products in the Orange Book and Drugs@FDA, and therefore the identity of the active ingredient for Venofer has also changed from "Iron Sucrose" to "Ferric Oxyhydroxide" in Orange Book and Drugs@FDA. With further such updates anticipated in the USP and RLD labeling, there will be, among other changes, labeling implication such as with the presentation of the established name, as the generic drug products would need to be consistent with the USP designation and RLD labeling. Therefore, the Agency has determined to defer this review per 21 CFR 314.110 and issue the following comments to the applicant.

Cycle 4 Update 03/18/2025:

ANDA labeling is modeled after the RLD's S-038 labeling

The following deficiency was included in the Cycle 3 addendum review:

GENERAL COMMENTS: We acknowledge receipt of your amendment received on December 28, 2020, which was deferred per 21 CFR 314.110 and not reviewed for this action. You may incorporate applicable sections of the deferred amendment by specific reference as part of your response to the deficiencies cited in this letter.

On 04/17/2023, the application received a complete response letter (CRL) due to drug substance, drug product, and bioequivalence deficiencies. Our labeling deficiency was also included in the CRL. On 08/18/2023, the Applicant provided their complete response to the deficiencies included in the CRL. On 04/04/2024 the Applicant submitted revised labeling to be same as the RLD updated labeling. Furthermore, on 08/05/2024, the Applicant submitted revised labeling (b)(4)

(b)(4)

Deficiency Comments:

4.3 PATENTS AND EXCLUSIVITIES (C4)

The Orange Book was searched on 03/17/2025

Table 4 provides Orange Book patents for the Model Labeling (NDA021135) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	**Patent Number**	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact**
	N/A						

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling						
Strengths	**Exclusivity Code**	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact**
	N/A					

Reviewer Assessment:

Deficiency	**No Deficiency**	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has **expired** and the applicant needs to revise labeling.
Reviewer Comments: **Deficiency Comments:**		

4.4 UNITED STATES PHARMACOPEIA (USP) (C4)

The USP was searched on 03/17/2025

Table 6: USP				
	YES or NO	**Date**	**Monograph Title (N/A if no monograph)**	**Packaging and Storage/Labeling Statements (N/A if no monograph)**
Currently Official	Yes	[redacted]	Iron Sucrose Injection	ADDITIONAL REQUIREMENTS Change to read: •Packaging and Storage: Preserve in single-dose containers▲ , preferably▲ (RB 1-Apr-2023)of Type I glass. Store at controlled room temperature. Do not freeze.

Table 6: USP				
	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
				•Labeling: Label it to indicate that it is for intravenous use only, and that when administered by intravenous infusion, the Injection must be diluted with 0.9% Sodium Chloride Injection to a concentration of 1.0–2.0 mg/mL of elemental iron. Label it also to state the total osmolarity of the solution expressed in mOsmol/L.
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	**Established name** is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary **name is different from USP** established name.
☒	☐	**USP descriptor** is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	**DISSOLUTION**: The applicant's dissolution statement is appropriate.
☐	☒	**ORGANIC IMPURITIES**: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	**ASSAY**: Drug product meets USP acceptance criteria for assay.

Reviewer Comments:

Deficiency Comments:

Deficiency # 1

Created in C4

Prescribing Information Response / Assessment:

HOW SUPPLIED/STORAGE AND HANDLING: Add the "USP" descriptor to the HOW SUPPLIED/STORAGE AND HANDLING section.

4.5 MODEL CONTAINER LABELS (C4)

Model container/carton/blister labels (Source: carton labeling: ANRPT-21 (submitted on 12/16/2021) and ANRPT-24 (submitted 12/18/2024); container label: ANRPT-20 (submitted on 12/17/2020) **)**


NDC 0517-2325-01
Venofer®
(Iron Sucrose) Injection, USP
50 mg Elemental Iron per 2.5 mL (20 mg/mL)
2.5 mL Single-Dose Vial
Discard Unused Portion
For Intravenous Use Only
Rx Only
Each 2.5 mL contains: 50 mg elemental iron (as iron sucrose) in water for injection. The drug product contains approximately 30% sucrose w/v (300 mg/mL). pH 10.5 to 11.1. Osmolarity 1,250 mOsmol/L. Contains no preservatives. Store at 20° to 25°C (68° to 77°F). Rev. 7/2020
AMERICAN REGENT, INC.
SHIRLEY, NY 11967
Lot / Exp.
NDC 0517-2340-01
Venofer®
(Iron Sucrose) Injection, USP
100 mg Elemental Iron per 5 mL (20 mg/mL)
5 mL Single-Dose Vial
Discard Unused Portion
For Intravenous Use Only
Rx Only
Each 5 mL contains: 100 mg elemental iron (as iron sucrose) in water for injection. The drug product contains approximately 30% sucrose w/v (300 mg/mL). pH 10.5 to 11.1. Osmolarity 1,250 mOsmol/L. Contains no preservatives. Store at 20° to 25°C (68° to 77°F). Rev. 7/2020
AMERICAN REGENT, INC.
SHIRLEY, NY 11967
Lot / Exp.
NDC 0517-2310-01
Venofer®
(Iron Sucrose) Injection, USP
200 mg Elemental Iron per 10 mL (20 mg/mL)
10 mL Single-Dose Vial
Discard Unused Portion
For Intravenous Use Only
Rx Only
Each 10 mL contains: 200 mg elemental iron (as iron sucrose) in water for injection. The drug product contains approximately 30% sucrose w/v (300 mg/mL). pH 10.5 to 11.1. Osmolarity 1,250 mOsmol/L. Contains no preservatives. Store at 20° to 25°C (68° to 77°F). Rev. 7/2020
AMERICAN REGENT, INC.
SHIRLEY, NY 11967
Lot / Exp.
Venofer
iron sucrose injection USP
200 mg Elemental Iron per 10 mL (20 mg/mL)
NDC 0517-2310-05
5 x 10 mL
Single-Dose Vials
10 mL Single-Dose Vial • Discard Unused Portion
Rx Only
For Intravenous Use Only
AMERICAN REGENT, INC.
SHIRLEY, NY 11967
Rev. 3/2021
Venofer
10 mL
Single-Dose Vial
For Intravenous Use Only

5 ASSESSMENT OF ANDA LABELING AND LABELS (C4)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C4)

5.1.1 DRUG PRODUCT REVIEW (C4)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review pending

Comments from C2 Labeling Review
"CHEMISTRY is INADEQAUTE-MAJOR as of this labeling review cycle dated 4/14/2020."

C3 Labeling Review Updates
DP Review (Reference #44536490) is pending. Per the prescreen checklist, "List of Deficiencies: NA."

5.1.2 DESCRIPTION (C4)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	Each mL contains 20 mg elemental iron as iron sucrose in water for injection. Venofer is available in 5 mL single-dose vials (100 mg elemental iron per 5 mL). The drug product contains approximately 30% sucrose w/v (300 mg/mL). Sodium hydroxide may be added to adjust pH to 10.5 to 11.1. The product contains no preservatives. The osmolarity of the injection is 1,250 mOsmol/L.
Previous ANDA Labeling	(b)(4)
Current ANDA Labeling	

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C4)

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	16.1 How Supplied Venofer is supplied sterile in 5 mL single-dose vials. Each 5 mL vial contains 100 mg elemental iron (20 mg/mL). NDC-0517-2340-99 100 mg/5 mL Single-Dose Vial Packages of 10 16.2 Stability and Storage Contains no preservatives. Store in original carton at 20° to 25°C (68° to 77° F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not freeze. Syringe Stability: Venofer, when diluted with 0.9% NaCl at concentrations ranging from 2 mg to 10 mg of elemental iron per mL, or undiluted (20 mg elemental iron per mL) and stored in a plastic syringe, was found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C) and under refrigeration (4°C ± 2°C). Intravenous Admixture Stability: Venofer, when added to intravenous infusion bags (PVC or non-PVC) containing 0.9% NaCl at concentrations ranging from 1 mg to 2 mg of elemental iron per mL, has been found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C). Do not dilute to concentrations below 1 mg/mL. Do not mix Venofer with other medications or add to parenteral nutrition solutions for intravenous infusion. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to infusion.
Previous ANDA Labeling	(b)(4)

Table 8: Comparison of Model Labeling to ANDA Labeling	
	(b)(4)
Current ANDA Labeling	(b)(4)

Table 8: Comparison of Model Labeling to ANDA Labeling	
	(b)(4)

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C4)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements		
Previous ANDA Labeling		
Name and Address on ANDA Prescribing Information	(b)(4)	
Current ANDA Labeling		
Name and Address on ANDA Prescribing Information	Manufactured by Rafarm S.A. for Sandoz Inc., Princeton, NJ 08540 **Reviewer Assessment:** (b)(4) Acceptable.	

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements			
Manufactured by	**Manufactured for**	**Distributed by**	**Distributed for**

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the **too small exemption** [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
		ESTABLISHED/PROPRIETARY NAME and STRENGTH:
☐	☒	**Tall Man** lettering complies with recommendations found on FDA webpage.
☒	☐	Established/proprietary **name and strength are the most prominent** information on the Principal Display Panel.
☐	☒	No **intervening text**(written, printed, or graphic matter) between established name and strength.
		THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:
☐	☒	**Net quantity** statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Dosage** statement.
☐	☒	**NDC number:** prominence, linear bar code, and its orientation.
☐	☒	**Expiration date and lot number** (or placeholder).
☐	☒	**Equivalency statement** (product strength).
☐	☒	**Medication Guide** Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol.
☐	☒	**Image of drug product** represents the true size, color, and imprint.
☐	☒	**Yellow #5** (tartrazine) warning statement is properly displayed.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Latex** warning statement is properly displayed [21 CFR 801.437.].

Deficiency	No Deficiency	
☐	☒	**Gluten** statement is appropriately stated.
	PRODUCT DIFFERENTIATION:	
☐	☒	ANDA is the **same color** as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple **strengths are differentiated** by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from **related products**.
	STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:	
☐	☒	**Storage/dispensing** statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe **container closure**, cite source, and any issues in Reviewer Comments below.
	OVERALL ASSESSMENT:	
☒	☐	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Cycle 3:

The container labels and carton labeling were found acceptable in the C2 Labeling Review ; however, RLD container labels and carton labeling were revised in NDA 021135/S-037 (see Section 3.3 below). No new deficiencies are identified; thus, the ANDAs previously proposed container labels and carton labeling are satisfactory.

Cycle 4 Update 03/18/2025:

Related Products: Searched "iron sucrose" and "Sandoz" in CDEROne Nexus and did not identify any related products marketed by the Applicant.

Container closure: (b)(4)

(b)(4)

Deficiency Comments:

Deficiency # 1 Created in C4 Container Label Response / Assessment:	Decrease the prominence of the net quantity statement (i.e., 2.5 mL Single-Dose Vial, 5 mL Single-Dose Vial, 10 mL Single-Dose Vial) on all container labels so that it does not compete with the most critical information (e.g., established name, strength, route of administration, etc.), on the principal display panel (PDP). Refer to the Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors | FDA.
Deficiency # 2 Created in C4 Container Label Response / Assessment:	Revise the route of administration to title case (i.e., "For Intravenous Use Only") to be same as the RLD.

5.2.1 INJECTABLE PRODUCTS (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Appropriate **package type term** was used (e.g. multiple-dose, single-dose, single-patient-use).
☐	☒	Product label states, "**Discard unused portion**" for single dose products.
☐	☒	IV, IM, or SC was spelled out.
☐	☒	There is **text on the cap/ferrule** overseal of this injectable product. If "Yes", does the text comply with the recommendations in USP General Chapter <7> Labeling.
☐	☒	The **cap color** is Green for the 50 mg vial and Purple for the 100 mg and 200 mg strength vial . ***NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.***
Reviewer Comments: **Deficiency Comments:**		

5.2.1.1 CONTAINER LABEL FOR PARENTERAL SOLUTIONS (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	**Strength** expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP General Chapter <7> Labeling.
☐	☒	If volume is less than 1 mL, **strength per fraction of a milliliter** is the only expression of strength.
☐	☒	Quantity or proportion of all **inactive ingredients** listed on label as required under 1 CFR 201.100(b)(5)(iii).
☐	☒	Container label includes **instructions for reconstitution** if applicable.
☐	☒	**Aluminum content** is present on immediate container label (SVP, LVP, or PBP) and **warning** is present in the prescribing information.
Reviewer Comments: **Deficiency Comments:**		

5.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	**Unit-Dose Carton expression of strength** appropriately stated.
☒	☐	The answers to the Container Label questions are the same for the Carton Labeling. Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments: **Deficiency Comments:** Deficiency # 1 Created in C4 Carton Labeling Response / Assessment:		Side Panel: Add the word "Sterile" following the storage temperatures on all carton labeling to be same as the RLD.

Deficiency # 2 Created in C4 Carton Labeling Response / Assessment:	Side Panel: Revise (b)(4) to "Sodium hydroxide may be added to adjust pH to 10.5 to 11.1." on all carton labeling to be same as the RLD.
Deficiency # 3 Created in C4 Carton Labeling Response / Assessment:	Refer to the comment under 1b.

5.4 PRESCRIBING INFORMATION (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
	HIGHLIGHTS:	
☐	☒	**Contact information** for applicant and FDA are listed correctly.
☐	☒	**Revision date** appears at the end of HIGHLIGHTS section (PLR) or end of prescribing information (non-PLR).
	DESCRIPTION/INACTIVE INGREDIENTS:	
	Appropriate **warning/precaution** statements for inactive ingredients are present (21 CFR 201) Check only if applicable:	
☐	☒	☐ Sulfite (21 CFR 201.22) ☐ Yellow #5 (Tartrazine) (21 CFR 201.20) ☐ Phenylalanine/aspartame (21 CFR 201.21) ☐ Latex (21 CFR 801.437).
☐	☒	**Sterile** product statement [21 CFR 201.57(c)(12)(i)(D)].
☐	☒	☐ **Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	☐ **Gluten** statement is appropriately stated.
☐	☒	**Dosage form, pharmacologic/therapeutic class, and route** of administration properly listed [21 CFR 201.57(c)(12)(i)(B)] and[21 CFR 201.57(c)(12)(i)(E)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	All **submitted labels** and labeling are consistent with the HOW SUPPLIED section.
☒	☐	**Physical description** (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	**NDC** numbers are present.
☐	☒	Drug product is the **same color** as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	**Storage or dispensing** statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☒	☐	**"Discard unused portion"** for single-dose products.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
	REGULATORY/OVERALL ASSESSMENT:	
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the **Antiretroviral Pregnancy Registry** (APR) upon full approval.
☐	☒	**Pregnancy registry** information is appropriately included/excluded as required for the RLD.

Deficiency	No Deficiency	
☐	☒	**Patent/exclusivity** carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Dosage form/strength** carve out (RLD combined labeling): justification for retaining information for safety/efficacy.
☐	☒	Prescribing information meets **formatting requirements** [21 CFR 201.57 (PLR) or 21 CFR 201.80 (non-PLR)].
☒	☐	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Deficiency Comments:

Deficiency # 1 Created in C4 Prescribing Information Response / Assessment:	HOW SUPPLIED/ STORAGE AND HANDLING: Add your product description (e.g., shape, color, scoring, coating, and imprint code) to be in accordance with the information in your submission, as required per 21 CFR 201.57(c)(17).
Deficiency # 2 Created in C4 Prescribing Information Response / Assessment:	HOW SUPPLIED/STORAGE AND HANDLING: Add "Discard unused portion" to this section as the proposed product is for a single-dose container. Refer to the Guidance for Industry - Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Container for Human Use.

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C4)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☒	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:

Comments from C2 Labeling Review

"Questions to the chemist:
Did the firm submit **studies that support** the following found in the Prescribing Information?

Syringe Stability: Iron sucrose injection, when diluted with 0.9% NaCl at concentrations ranging from 2 mg to 10 mg of elemental iron per mL, or undiluted (20 mg elemental iron per mL) and stored in a plastic syringe, was found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C) and under refrigeration (4°C ± 2°C).

Intravenous Admixture Stability: Iron sucrose injection, when added to intravenous infusion bags (PVC or non-PVC) containing 0.9% NaCl at concentrations ranging from 1 mg to 2 mg of elemental iron per mL, has been found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C)."

- **RESPONSE**: "The firm did provide compatibility study data. Please see my assessment of the study on page 52-53 of my DP quality review. The compatibility data is adequate."

Deficiency Comments:

Cameron Clark

Digitally signed by Cameron Clark
Date: 3/24/2025 01:58:04PM
GUID: 5a4fa1f0001c26bc28df0e20df234537

Ellen Hwang

Digitally signed by Ellen Hwang
Date: 3/24/2025 02:43:47PM
GUID: 5256bdc00002af3bc3fa942a9512a891

[redacted]

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	July 16, 2021, and August 26, 2021
ANDA Number(s)	212340
Review Number	3 - Addendum
Applicant Name	Sandoz Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Iron Sucrose Injection USP, 50 mg Elemental Iron/2.5 mL (20 mg/mL), 100 mg Elemental Iron/5 mL (20 mg/mL) and 200 mg Elemental Iron/10 mL (20 mg/mL), Single-Dose Vials
Proposed Proprietary Name	None
Submission Received Date	December 28, 2020
Primary Labeling Reviewer	Susan Rimmel, PharmD
Secondary Labeling Reviewer	Refer to signature page

Review Conclusion

☐ ACCEPTABLE – No Comments
☐ ACCEPTABLE – Include Post Approval Comments
☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant
☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No (If yes, indicate ANDA number)

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling deficiencies based on your submission received December 28, 2020:

GENERAL COMMENTS: We acknowledge receipt of your amendment received on December 28, 2020, which was deferred per 21 CFR 314.110 and not reviewed for this action. You may incorporate applicable sections of the deferred amendment by specific reference as part of your response to the deficiencies cited in this letter.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission (s) received (add date)

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).
Click here to enter text.

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

Reviewer Comments: The comments below are from the **C2 Labeling Review** based on the submission received 10/31/2019, and DLRs **Assessment**.

"The Division of Labeling has **no further questions/comments** at this time based on your labeling submission(s) received 10/31/2019." "These comments will be addressed **post approval** (in the first labeling supplement review)."

> "**Prescribing Information** -
> Please correct the **revisions date** to reflect the recent revisions at the end of the HIGHLIGHTS of PRESCRIBING INFORMATION and HOW SUPPLIED sections. (Revise from (b)(4) to "10/2019")"

- **Assessment**: The revised proposed labeling is in **PLR format**. Per Guidance, the **revision date at the end of the Highlights** section **replaces the revision date at the end of labeling** in the **old format** and is **not required** (i.e., after Section 17). Additionally, the revision date is the date of approval for original approval applications. For tracking purposes, it is **reasonable for Applicants to use** the revision **date they anticipate FDA will receive the submission**, as suggested in the post-approval comment above. However, it is **common practice for Applicant's to revise labeling in advance** of their submission and utilize a revision date that differs from the FDA received date. Thus, the post-approval deficiency above is not provided to the Applicant but **new deficiencies** were identified (**see Recommendation below and Section 3.2 below**).

C3 Recommendation

1. PRESCRIBING INFORMATION, Highlights Title and Limitation Statement: The name of the drug product is not in uppercase letters to improve its prominence (e.g., "INJECTION" vs. "Injection").

Addendum
See Section 3.2 below.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

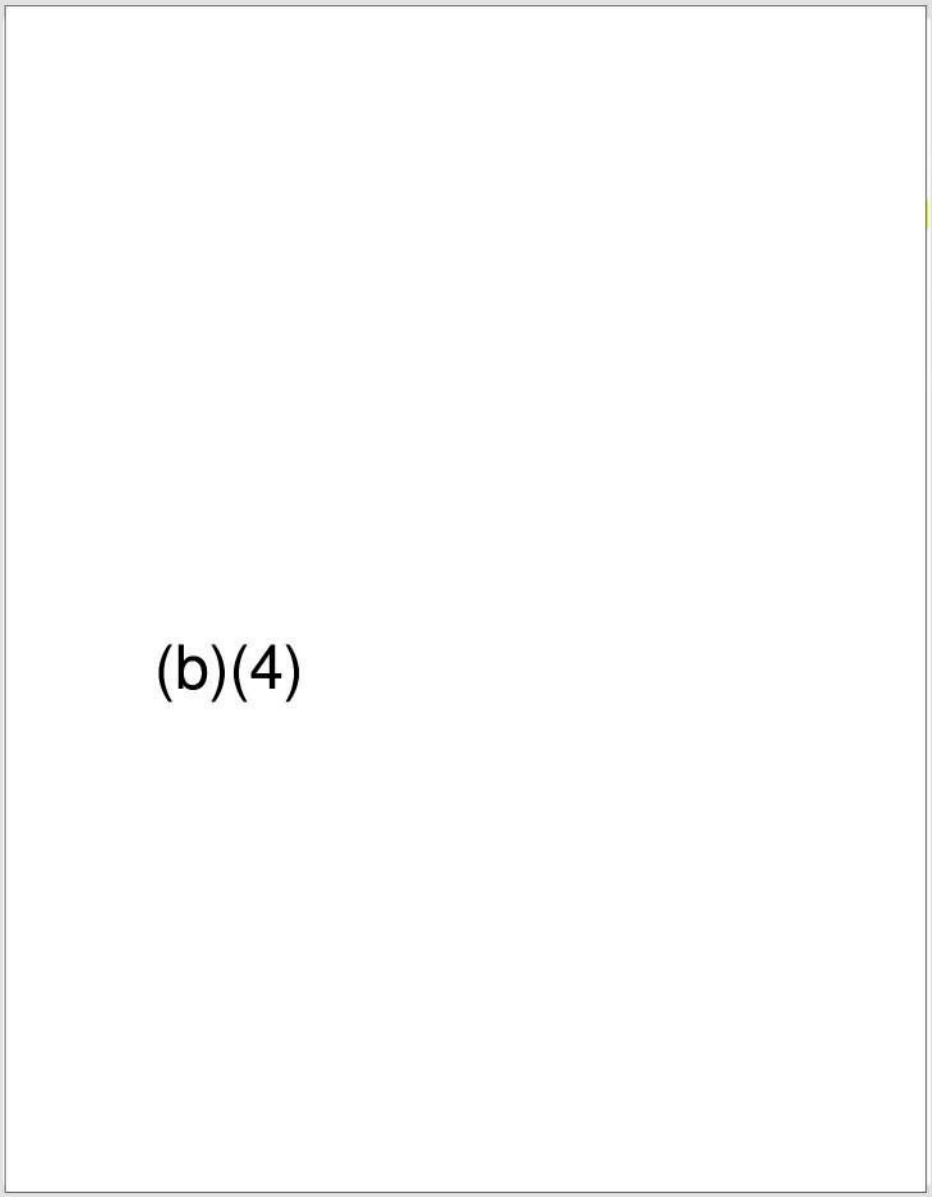
Reviewer Comments: The container labels and carton labeling were found acceptable in the C2 Labeling Review ; however, RLD container labels and carton labeling were revised in NDA 021135/S-037 (**see Section 3.3 below**). No new deficiencies are identified; thus, the ANDAs previously proposed container labels and carton labeling are satisfactory.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

Description of Container Closure (Module 3.2.P.7 Container Closure System, 8/28/2019)



Comments from C2 Labeling Review

"CHEMISTRY is **INADEQAUTE-MAJOR** as of this labeling review cycle dated 4/14/2020."

C3 Labeling Review Updates

DP Review (Reference #44536490) is pending. Per the prescreen checklist, "List of Deficiencies: NA."

- **Addendum**
  See Section 3.2 below.

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? NO
If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? YES

If Yes, please explain.

Docket #	Brand Name (or Drug Class)	Generic Name / Dosage Form / Strengths	Action Requested or Issue Description	RLD#	Approval Actions (TA/AP)	Communications (CRL, CC/IR/DRL)	Notes	Date Filed (~)	OGD Policy Lead
FDA-2020-P-0158	Multiple: iron sucrose products	Multiple: iron sucrose products	Requests FDA: 1) issue guidance, and publicly affirm, that the ANDA approval pathway is not appropriate for harder-to- copy complex drugs already identified by FDA; 2) that FDA's planned guidance on therapeutic equivalence for follow-on drugs approved pursuant to Section 505(b)(2)4 make clear that a follow-on harder-to-copy complex drug may be determined to be therapeutically equivalent to its reference listed drug ("RLD"), when the two drugs meet the existing criteria, namely, they have: (1) the same active ingredient; (2) the same route of administration, dosage form, and strength; (3) the same clinical effect and safety profile; and (4) been shown to be bioequivalent	multiple	See Notes Column >>	No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL for Filing or Quality prior to contacting Policy Lead	(b)(4)	1/10/2020	Geeta Daniel
FDA-2005-P-0319 (2005P-0095)	Venofer	Iron Sucrose Injection	Requests FDA to require identical manufacturing process, physico-chemical properties, BE standards.	021135	No Approval Actions (TA/AP) can be taken prior to contacting Policy Lead	No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL for Bioequivalence or Quality prior to contacting Policy Lead		9/9/2005	Geeta Daniel

Addendum
See Section 3.2 below for information related to the CP above.

Is the drug product listed on the Susceptibility Test Interpretive Criteria web page? NO

3.2 MODEL LABELING

Table 1: Review Model Labeling
(Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so enter the most recently approved ANDA labeling information as applicable.)

NDA# /Supplement# (S-000 if original): 021135/S-037

Supplement Approval Date: 1/20/2021

Proprietary Name: Venofer

Table 1: Review Model Labeling (Check the box used as the Model Labeling)
Established Name: iron sucrose injection (b)(4)
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:**
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.
☐ **OTHER (Describe):** Click here to enter text.

Reviewer Assessment:

Is the Prescribing Information or Drug Facts Labeling (OTC) same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **NO**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old), or 201.66 (OTC)? **NO**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments: The ANDAs revised proposed labeling is based on NDA 021135/S-036; thus, a deficiency is issued (**see Recommendation below**).

C3 Recommendation

1. GENERAL COMMENTS: The revised proposed labeling is not in accordance with the labeling for the Reference Listed Drug (RLD), Venofer injection, NDA 021135/S-037 approved on January 20, 2021, found on the Drugs@FDA website. Additional preliminary comments are provided but not inclusive of all the revisions that may be needed.

Internal

An internal meeting was held on 07/16/2021 between DLR, OPQ, and OGDP to discuss the implication of Velphoro CP response (Docket No. FDA-2016-P-1163; 5/26/2021) which clarified that the active ingredient for the drug products containing ferric oxyhydroxide (iron(III) oxyhydroxide) and carbohydrate sugars is "Ferric Oxyhydroxide". This determination has so far changed the identity of the active ingredient for the iron carbohydrate drug products in the Orange Book and Drugs@FDA, and therefore the identity of the active ingredient for Venofer has also changed from "Iron Sucrose" to "Ferric Oxyhydroxide" in Orange Book and Drugs@FDA. With further such updates anticipated in the USP and RLD labeling, there will be, among other changes, labeling implication such as with the presentation of the established name, as the generic drug products would need to be consistent with the USP designation and RLD labeling. Therefore, the Agency has determined to defer this review per 21 CFR 314.110 and issue the following comments to the applicant.

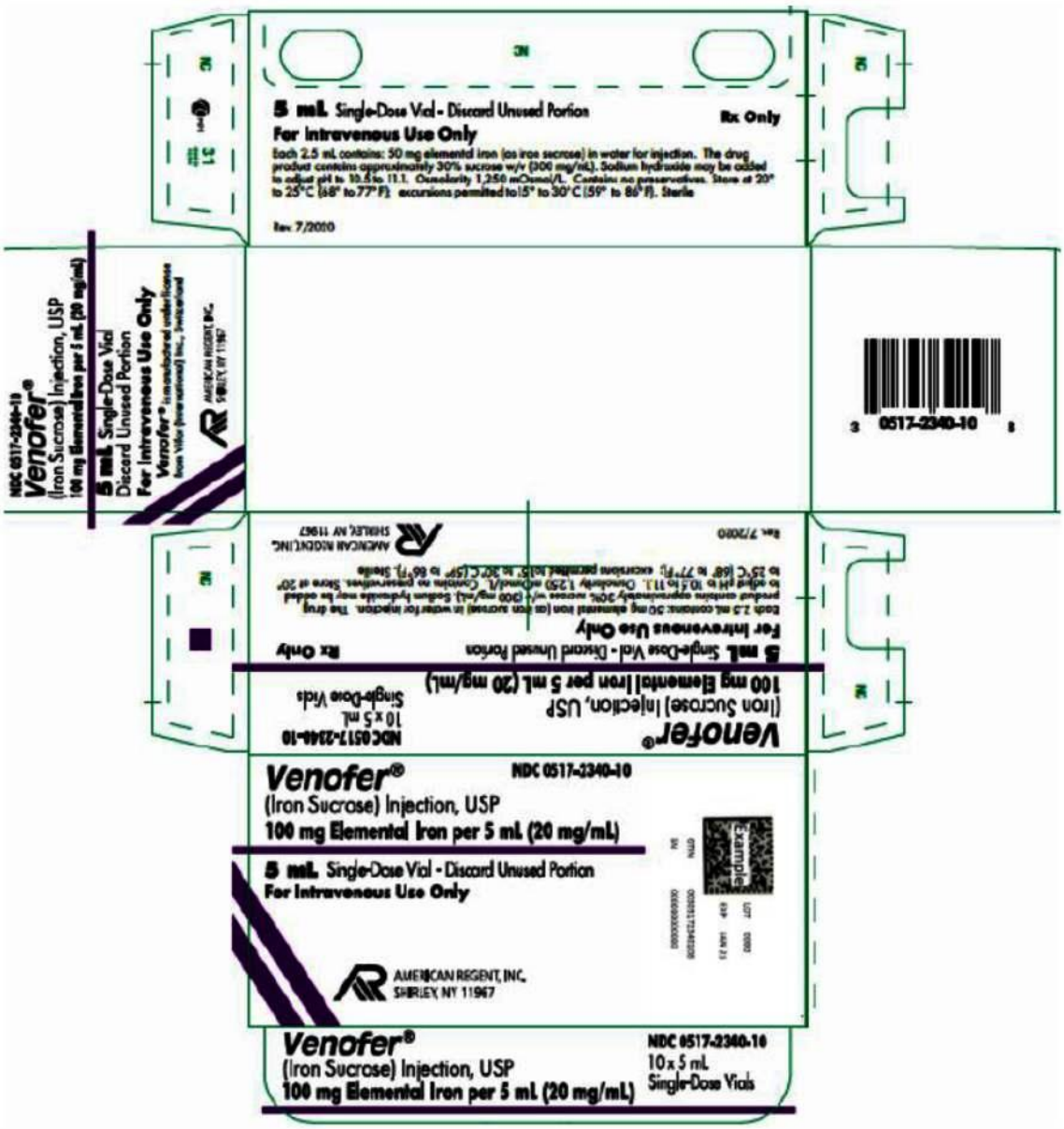
> "GENERAL COMMENTS: We acknowledge receipt of your amendment received on December 28, 2020, which was deferred per 21 CFR 314.110 and not reviewed for this action. You may incorporate applicable sections of the deferred amendment by specific reference as part of your response to the deficiencies cited in this letter."

3.3 MODEL CONTAINER LABELS

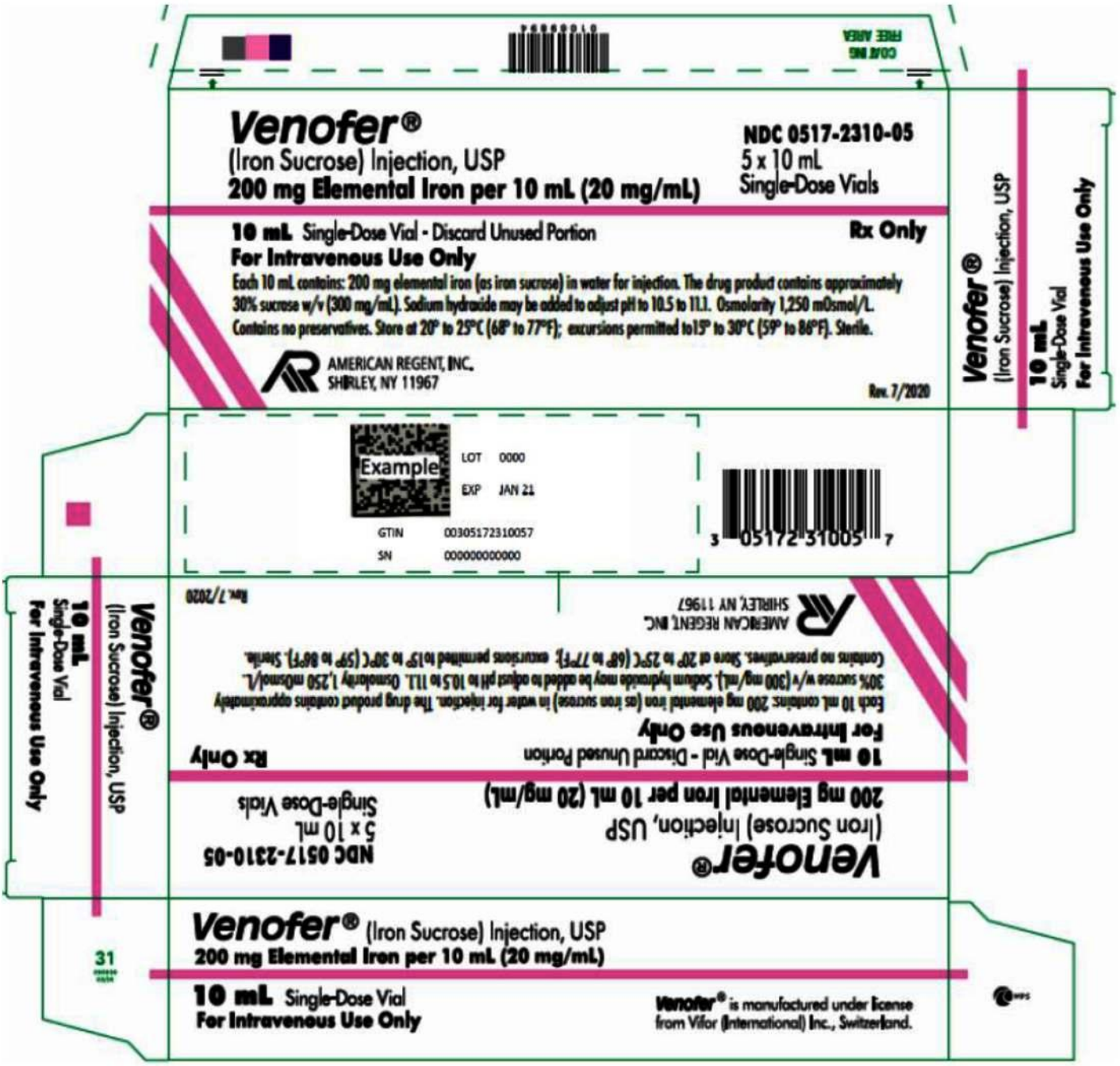
Model container/carton/blister labels

- **Marketed Strengths (20 mg/mL) and Packaging Configurations (SDVs)**
  - **50 mg/2.5 mL**: 10 x 2.5 mL
  - **100 mg/5 mL**: 1 x 5 mL, 10 x 5mL, and 25 x 5 mL
  - **200 mg/10 mL**: 5 x 10 mL

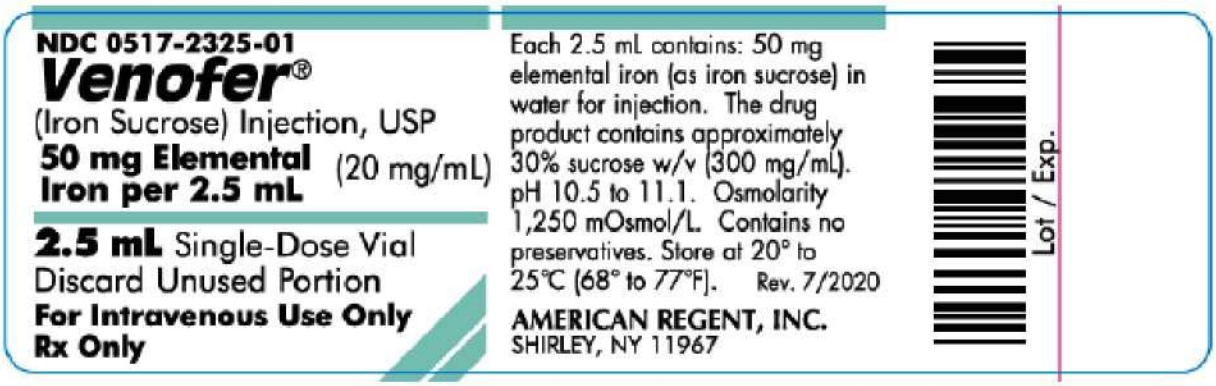
Approved (Source: S-037, FINAL received in EDR 1/19/2021, approved 1/20/2021)

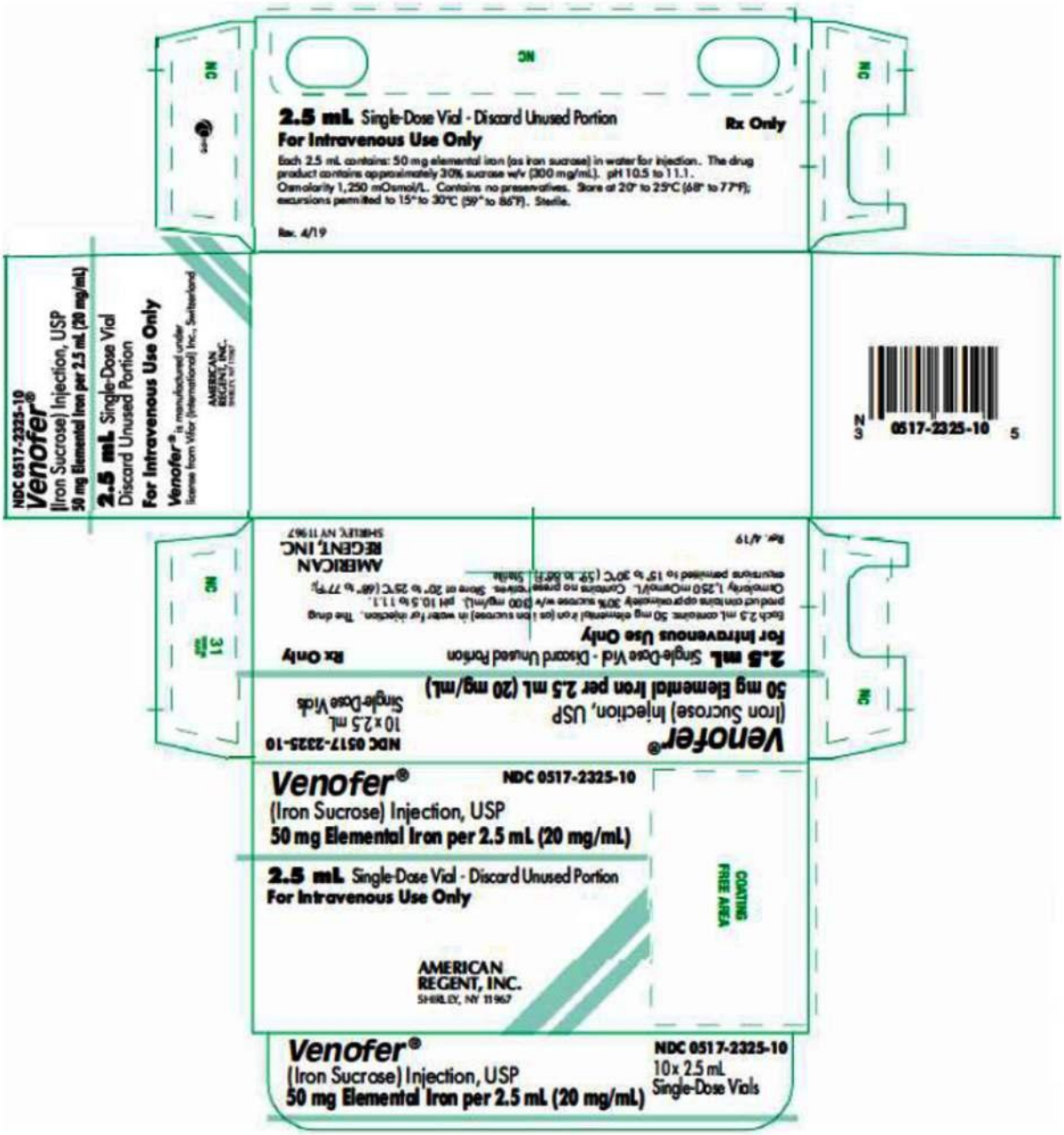


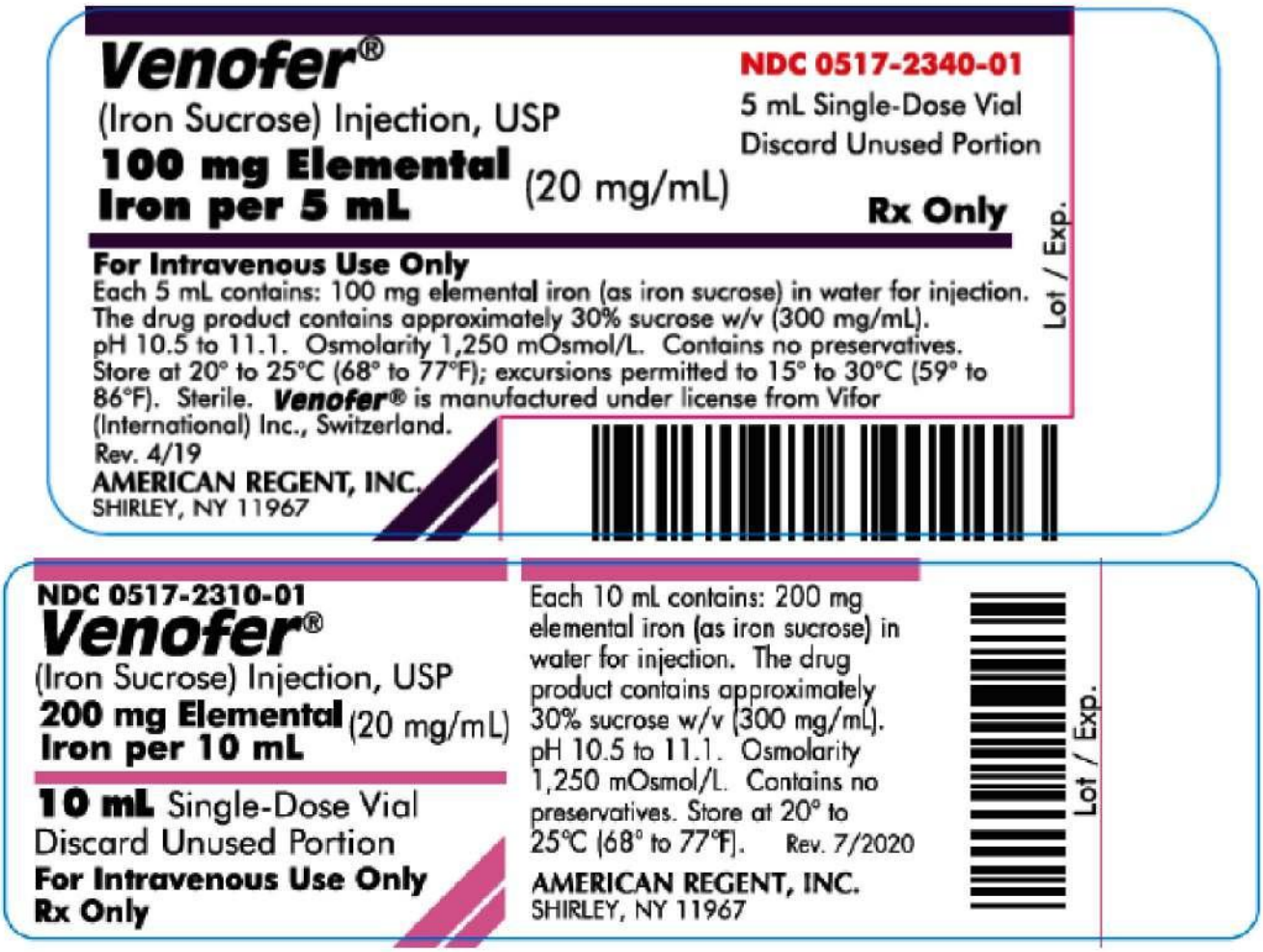

Venofer®
(Iron Sucrose) Injection, USP
100 mg Elemental Iron per 5 mL (20 mg/mL)
NDC 0517-2340-25
25 x 5 mL Single-Dose Vials
Discard Unused Portion
Rx Only
For Intravenous Use Only
Each 5 mL contains: 100 mg elemental iron (as iron sucrose) in water for injection. The drug product contains approximately 30% sucrose w/v (300 mg/mL). Sodium hydroxide may be added to adjust pH to 10.5 to 11.1. Osmolarity 1,250 mOsmol/L. Contains no preservatives. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). Sterile.
Venofer® is manufactured under license from Vifor (International) Inc., Switzerland.
AMERICAN REGENT, INC.
SHIRLEY, NY 11967
Rev. 7/2020
Lot / Exp.
XXXX JAN21


Venofer®
(Iron Sucrose) Injection, USP
200 mg Elemental Iron per 10 mL (20 mg/mL)
NDC 0517-2310-05
5 x 10 mL
Single-Dose Vials
10 mL Single-Dose Vial - Discard Unused Portion
Rx Only
For Intravenous Use Only
Each 10 mL contains: 200 mg elemental iron (as iron sucrose) in water for injection. The drug product contains approximately 30% sucrose w/v (300 mg/mL). Sodium hydroxide may be added to adjust pH to 10.5 to 11.1. Osmolarity 1,250 mOsmol/L. Contains no preservatives. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). Sterile.
AMERICAN REGENT, INC.
SHIRLEY, NY 11967
Rev. 7/2020
Example
LOT 0000
EXP JAN 21
GTIN 00305172310057
SN 000000000000
3 05172 31005 7
Venofer®
(Iron Sucrose) Injection, USP
10 mL
Single-Dose Vial
For Intravenous Use Only
31
Venofer® is manufactured under license from Vifor (International) Inc., Switzerland.

Marketed (Source: ANRPT-20, FINAL, 12/17/2020)







3.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 7/17/2021.

Table 2: United States Pharmacopeia (USP)				
	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	YES	[redacted]	Iron Sucrose Injection	(b)(4)
Not Yet Official	NO		NA	NA

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **Biopharmaceutics Review and/or Drug Product Quality Review pending**

Reviewer Comments: None related to the C3 Labeling Review.

Comments from C2 Labeling Review

"BIOEQUIVALENCE is **INADEQUATE-MAJOR** (in-progress) as of this labeling review cycle dated 4/14/2020."

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 7/17/2021.

Table 3 provides Orange Book patents for the Model Labeling NDA 021135 and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
N/A						

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments: None.

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
N/A					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments: None.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
Are there changes to the manufacturer/distributor/packer statements? **YES**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review (C2)	Currently Proposed	Assessment
(b)(4)		No Change

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review (C2)	Currently Proposed	Assessment
(b)(4)		No Change

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review (C2)	Currently Proposed	Assessment
(b)(4)		Revised (b)(4) which is satisfactory.

5. COMMENTS/CONSULTS FOR OTHER DISCIPLINES

Describe questions, issues and consults sent to and/or received from other discipline(s) (e.g., OPQ, OB, DCR):

Refer to the Consult Screening flow chart to determine any necessary consults.

(For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue). Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments: None related to the C3 Labeling Review.

Comments from C2 Labeling Review

"Questions to the chemist:
Did the firm submit **studies that support** the following found in the Prescribing Information?

Syringe Stability: Iron sucrose injection, when diluted with 0.9% NaCl at concentrations ranging from 2 mg to 10 mg of elemental iron per mL, or undiluted (20 mg elemental iron per mL) and stored in a plastic syringe, was found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C) and under refrigeration (4°C ± 2°C).

Intravenous Admixture Stability: Iron sucrose injection, when added to intravenous infusion bags (PVC or non-PVC) containing 0.9% NaCl at concentrations ranging from 1 mg to 2 mg of elemental iron per mL, has been found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C)."

- **RESPONSE**: "The firm did provide compatibility study data. Please see my assessment of the study on page 52-53 of my DP quality review. The compatibility data is adequate."

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column,

you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container (20 mg/mL)	Draft	**50 mg**: 2.5 mL **100 mg**: 5 mL **200 mg**: 10 mL	10/31/2019	**C2: Satisfactory** **C3: Satisfactory**
Blister	NA			
Carton	Draft	**50 mg/2.5 mL** and **100 mg/5 mL**: 10- and 25-count **200 mg/10 mL**: 5- and 10-count	10/31/2019	**C2: Satisfactory** **C3: Satisfactory**
(Other – specify)	NA			
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	9/2020	12/28/2020	Revise
Medication Guide	NA			
Patient Information	NA			

Susan Rimmel

Digitally signed by Susan Rimmel
Date: 8/27/2021 10:53:51AM
GUID: 57e14a7301fe42aa569d1859f813583c

Dinaxi Jetton

Digitally signed by Dinaxi Jetton
Date: 8/27/2021 12:50:17PM
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LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	July 16, 2021
ANDA Number(s)	212340
Review Number	3
Applicant Name	Sandoz Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Iron Sucrose Injection USP, 50 mg Elemental Iron/2.5 mL (20 mg/mL), 100 mg Elemental Iron/5 mL (20 mg/mL) and 200 mg Elemental Iron/10 mL (20 mg/mL), Single-Dose Vials
Proposed Proprietary Name	None
Submission Received Date	December 28, 2020
Primary Labeling Reviewer	Susan Rimmel, PharmD
Secondary Labeling Reviewer	Refer to signature page

Review Conclusion

☐ ACCEPTABLE – No Comments
☐ ACCEPTABLE – Include Post Approval Comments
☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant
☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☐ No (If yes, indicate ANDA number)

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling deficiencies based on your submission received December 28, 2020:

1. GENERAL COMMENTS: Revise your labeling to be in accordance with the labeling for the Reference Listed Drug (RLD), Venofer injection, NDA 021135/S-037 approved on January 20, 2021, found on the Drugs@FDA website. Additionally, preliminary comments are provided below but are not inclusive of all the revisions that may be needed.

2. PRESCRIBING INFORMATION, Highlights Title and Limitation Statement: Revise the name of your drug product to uppercase letters to improve its prominence (e.g., "INJECTION" vs. "Injection").

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission (s) received (add date)

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).
Click here to enter text.

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

Reviewer Comments: The comments below are from the **C2 Labeling Review** based on the submission received 10/31/2019, and DLRs **Assessment**.

"The Division of Labeling has **no further questions/comments** at this time based on your labeling submission(s) received 10/31/2019." "These comments will be addressed **post approval** (in the first labeling supplement review)."

> "**Prescribing Information** -
> Please correct the **revisions date** to reflect the recent revisions at the end of the HIGHLIGHTS of PRESCRIBING INFORMATION and HOW SUPPLIED sections. (Revise from "04/2019" to "10/2019")"

- **Assessment**: The revised proposed labeling is in **PLR format**. Per Guidance, the **revision date at the end of the Highlights** section **replaces the revision date at the end of labeling** in the **old format** and is **not required** (i.e., after Section 17). Additionally, the revision date is the date of approval for original approval applications. For tracking purposes, it is **reasonable for Applicants to use** the revision **date they anticipate FDA will receive the submission**, as suggested in the post-approval comment above. However, it is **common practice for Applicant's to revise labeling in advance** of their submission and utilize a revision date that differs from the FDA received date. Thus, the post-approval deficiency above is not provided to the Applicant but **new deficiencies** were identified (**see Recommendation below and Section 3.2 below**).

Recommendation

1. PRESCRIBING INFORMATION, Highlights Title and Limitation Statement: The name of the drug product is not in uppercase letters to improve its prominence (e.g., "INJECTION" vs. "Injection").

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments: The container labels and carton labeling were found acceptable in the C2 Labeling Review (**see Section 2 above**); however, RLD container labels and carton labeling were revised in NDA 021135/S-037 (**see Section 3.3 below**). No new deficiencies are identified; thus, the ANDAs previously proposed container labels and carton labeling are satisfactory.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the

correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

Description of Container Closure (Module 3.2.P.7 Container Closure System, 8/28/2019)

(b)(4)

Comments from C2 Labeling Review

"CHEMISTRY is **INADEQAUTE-MAJOR** as of this labeling review cycle dated 4/14/2020."

C3 Labeling Review Updates

DP Review (Reference #44536490) is pending. Per the prescreen checklist, "List of Deficiencies: NA."

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? NO
If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? YES

If Yes, please explain.

Docket #	Brand Name (or Drug Class)	Generic Name / Dosage Form / Strengths	Action Requested or Issue Description	RLD#	Approval Actions (TA/AP)	Communications (CRL, CC/IR/DRL)	Notes	Date Filed (~)	OGD Policy Lead
FDA-2020-P-0158	Multiple: iron sucrose products	Multiple: iron sucrose products	Requests FDA: 1) issue guidance, and publicly affirm, that the ANDA approval pathway is not appropriate for harder-to- copy complex drugs already identified by FDA; 2) that FDA's planned guidance on therapeutic equivalence for follow-on drugs approved pursuant to Section 505(b)(2)4 make clear that a follow-on harder-to-copy complex drug may be determined to be therapeutically equivalent to its reference listed drug ("RLD"), when the two drugs meet the existing criteria, namely, they have: (1) the same active ingredient; (2) the same route of administration, dosage form, and strength; (3) the same clinical effect and safety profile; and (4) been shown to be bioequivalent	multiple	See Notes Column >>	No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL for Filing or Quality prior to contacting Policy Lead	(b)(4)	1/10/2020	Geeta Daniel
FDA-2005-P-0319 (2005P-0095)	Venofer	Iron Sucrose Injection	Requests FDA to require identical manufacturing process, physico-chemical properties, BE standards.	021135	No Approval Actions (TA/AP) can be taken prior to contacting Policy Lead	No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL for Bioequivalence or Quality prior to contacting Policy Lead		3/9/2005	Geeta Daniel

Is the drug product listed on the Susceptibility Test Interpretive Criteria web page? NO

3.2 MODEL LABELING

Table 1: Review Model Labeling
(Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so enter the most recently approved ANDA labeling information as applicable.)

NDA# /Supplement# (S-000 if original): 021135/S-037

Supplement Approval Date: 1/20/2021

Proprietary Name: Venofer

Established Name: iron sucrose injection

Description of Supplement: "This "Changes Being Effected in 30 days" supplemental new drug application provides for revised labeling for the drug product to include sodium hydroxide as a pH adjuster."

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

ANDA#/Supplement# (S-000 if original): Click here to enter text.

Table 1: Review Model Labeling (Check the box used as the Model Labeling)
Supplement Approval Date: Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:**
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.
☐ **OTHER (Describe):** Click here to enter text.

Reviewer Assessment:

Is the Prescribing Information or Drug Facts Labeling (OTC) same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **NO**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old), or 201.66 (OTC)? **NO**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments: The ANDAs revised proposed labeling is based on NDA 021135/S-036; thus, a deficiency is issued (**see Recommendation below**).

Recommendation

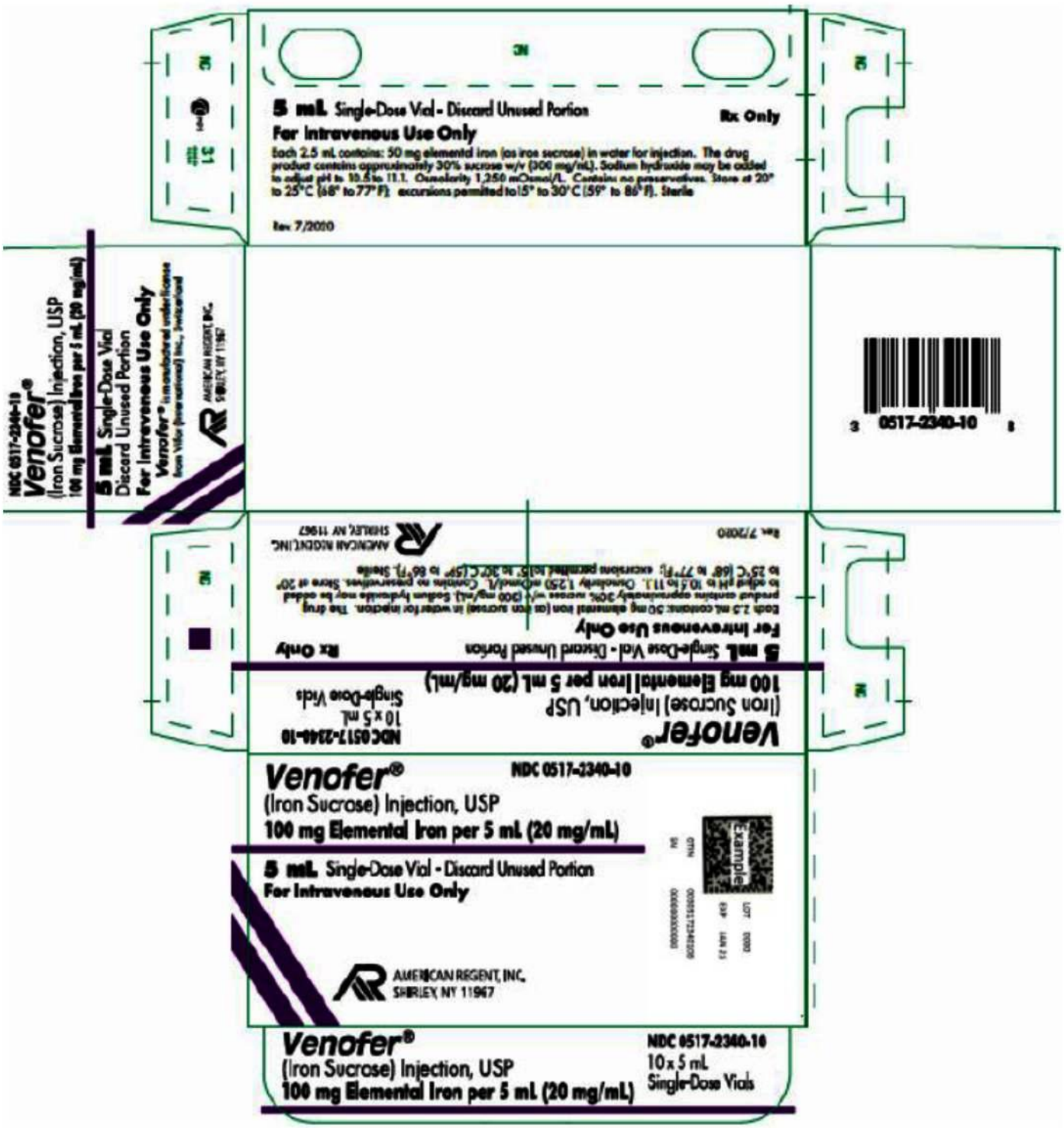
1. GENERAL COMMENTS: The revised proposed labeling is not in accordance with the labeling for the Reference Listed Drug (RLD), Venofer injection, NDA 021135/S-037 approved on January 20, 2021, found on the Drugs@FDA website. Additional preliminary comments are provided but not inclusive of all the revisions that may be needed.

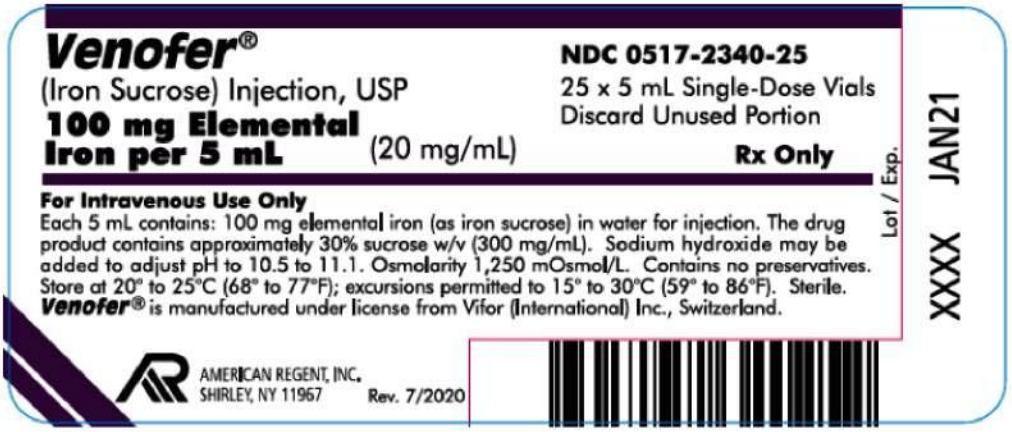
3.3 MODEL CONTAINER LABELS

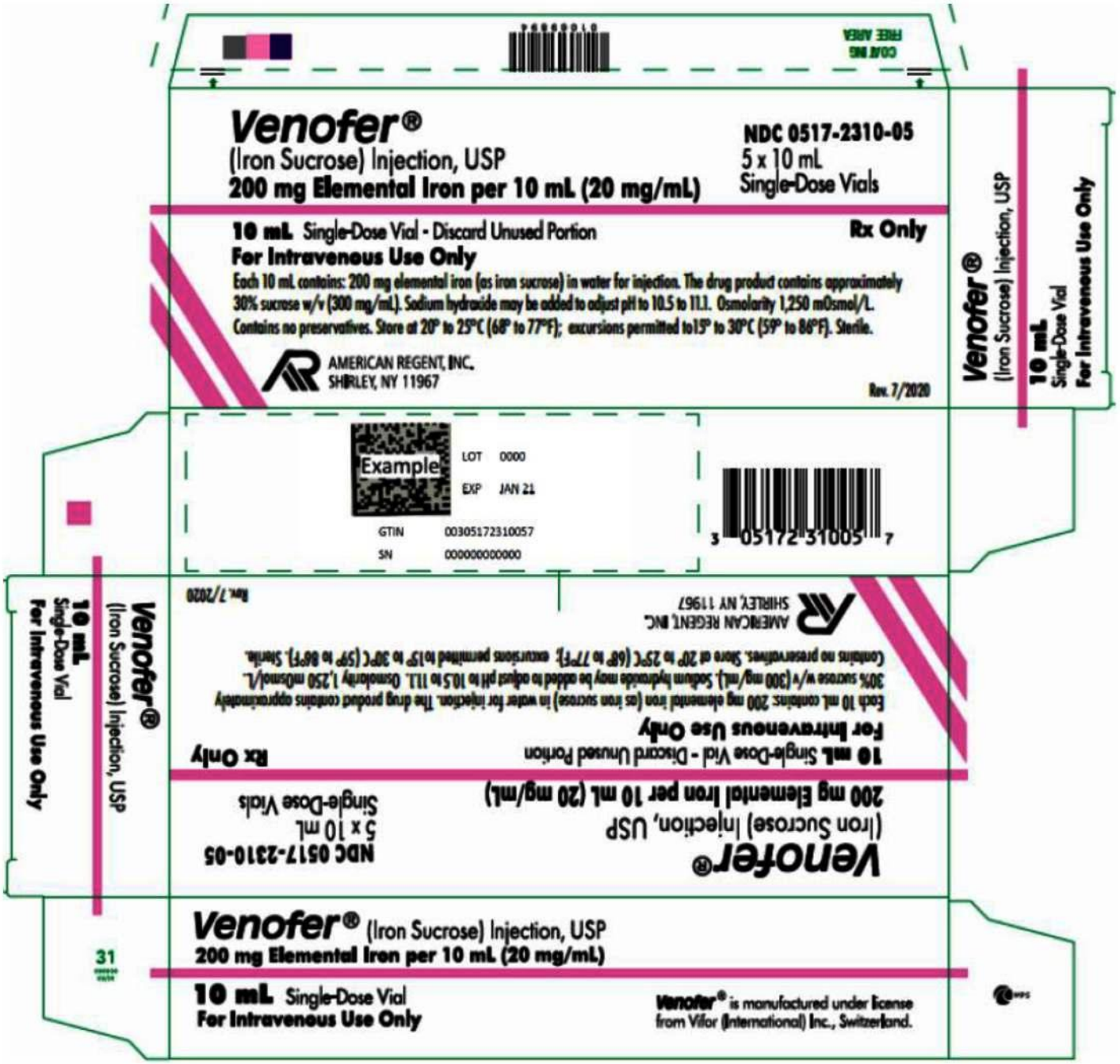
Model container/carton/blister labels

- **Marketed Strengths (20 mg/mL) and Packaging Configurations (SDVs)**
  - **50 mg/2.5 mL**: 10 x 2.5 mL
  - **100 mg/5 mL**: 1 x 5 mL, 10 x 5mL, and 25 x 5 mL
  - **200 mg/10 mL**: 5 x 10 mL

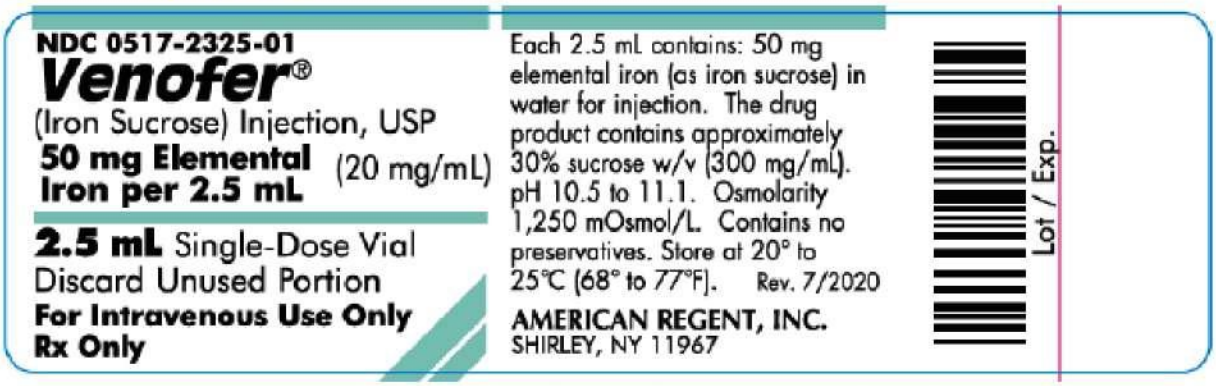
Approved (Source: S-037, FINAL received in EDR 1/19/2021, approved 1/20/2021)

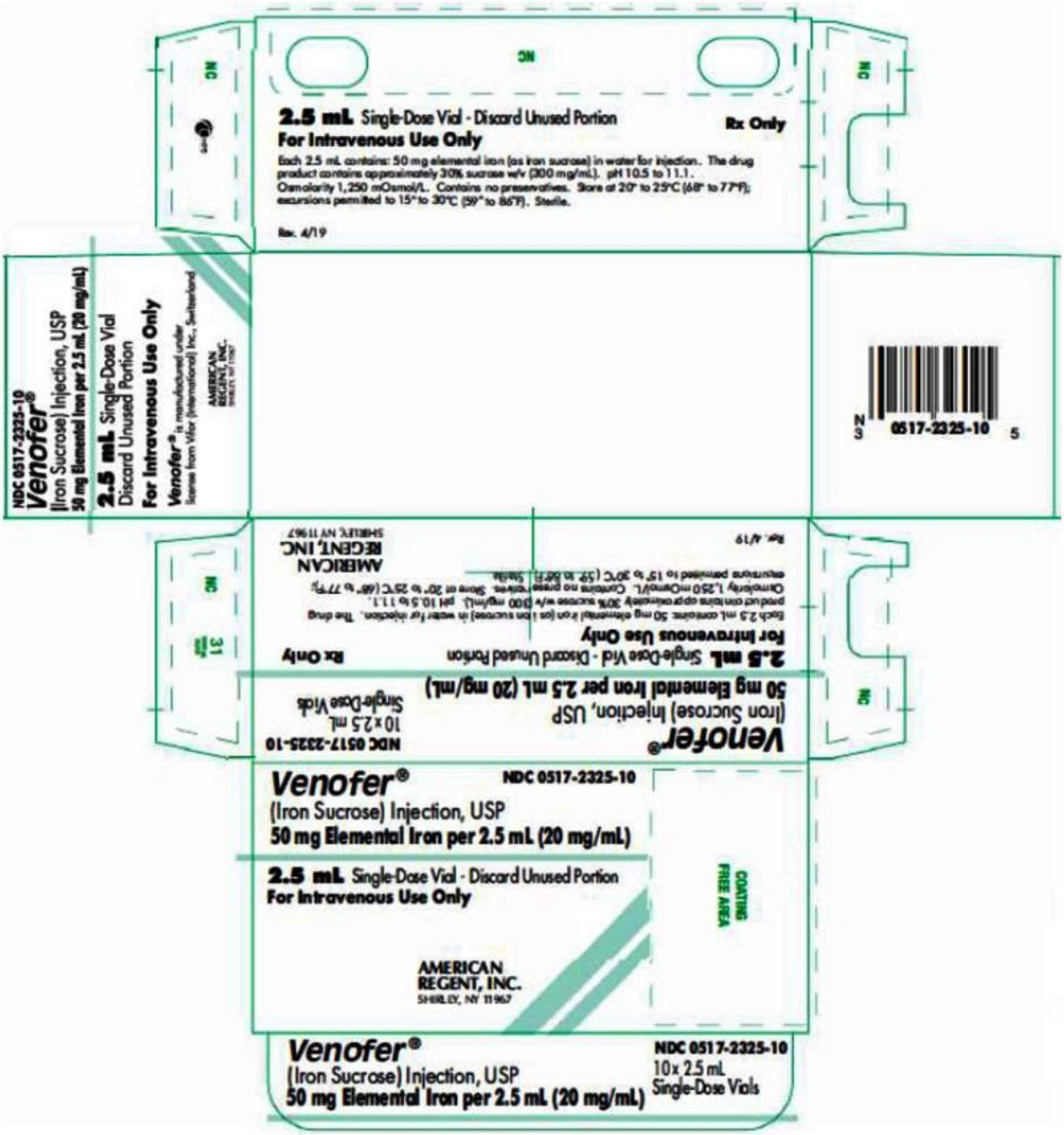

5 mL Single-Dose Vial - Discard Unused Portion
Rx Only
For Intravenous Use Only
Each 2.5 mL contains: 50 mg elemental iron (as iron sucrose) in water for injection. The drug product contains approximately 30% sucrose w/v (300 mg/mL). Sodium hydroxide may be added to adjust pH to 10.5 to 11.1. Osmolarity 1,250 mOsmol/L. Contains no preservatives. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). Sterile
Rev. 7/2020
NDC 0517-2340-10
Venofer®
(Iron Sucrose) Injection, USP
100 mg Elemental Iron per 5 mL (20 mg/mL)
5 mL Single-Dose Vial
Discard Unused Portion
For Intravenous Use Only
Venofer® is manufactured under license from Vifor (International) Inc., Switzerland
AMERICAN REGENT INC.
SHIRLEY, NY 11967
3 0517-2340-10 8
Example
LOT
EXP
Venofer®
(Iron Sucrose) Injection, USP
100 mg Elemental Iron per 5 mL (20 mg/mL)
NDC 0517-2340-10
10 x 5 mL
Single-Dose Vials


Venofer®
(Iron Sucrose) Injection, USP
100 mg Elemental Iron per 5 mL (20 mg/mL)
NDC 0517-2340-25
25 x 5 mL Single-Dose Vials
Discard Unused Portion
Rx Only
For Intravenous Use Only
Each 5 mL contains: 100 mg elemental iron (as iron sucrose) in water for injection. The drug product contains approximately 30% sucrose w/v (300 mg/mL). Sodium hydroxide may be added to adjust pH to 10.5 to 11.1. Osmolarity 1,250 mOsmol/L. Contains no preservatives. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). Sterile.
Venofer® is manufactured under license from Vifor (International) Inc., Switzerland.
AMERICAN REGENT, INC.
SHIRLEY, NY 11967
Rev. 7/2020
Lot / Exp.
XXXX JAN21


Venofer®
(Iron Sucrose) Injection, USP
200 mg Elemental Iron per 10 mL (20 mg/mL)
NDC 0517-2310-05
5 x 10 mL
Single-Dose Vials
10 mL Single-Dose Vial - Discard Unused Portion
Rx Only
For Intravenous Use Only
Each 10 mL contains: 200 mg elemental iron (as iron sucrose) in water for injection. The drug product contains approximately 30% sucrose w/v (300 mg/mL). Sodium hydroxide may be added to adjust pH to 10.5 to 11.1. Osmolarity 1,250 mOsmol/L. Contains no preservatives. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). Sterile.
AMERICAN REGENT, INC.
SHIRLEY, NY 11967
Rev. 7/2020
Example
LOT 0000
EXP JAN 21
GTIN 00305172310057
SN 000000000000
3 05172 31005 7
Venofer®
(Iron Sucrose) Injection, USP
10 mL
Single-Dose Vial
For Intravenous Use Only
31
Venofer® (Iron Sucrose) Injection, USP
200 mg Elemental Iron per 10 mL (20 mg/mL)
10 mL Single-Dose Vial
For Intravenous Use Only
Venofer® is manufactured under license from Vifor (International) Inc., Switzerland.

Marketed (Source: ANRPT-20, FINAL, 12/17/2020)





3.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 7/17/2021.

Table 2: United States Pharmacopeia (USP)

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	YES	[redacted]	Iron Sucrose Injection	(b)(4)
Not Yet Official	NO		NA	NA

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **Biopharmaceutics Review and/or Drug Product Quality Review pending**

Reviewer Comments: None related to the C3 Labeling Review.

Comments from C2 Labeling Review

"BIOEQUIVALENCE is **INADEQUATE-MAJOR** (in-progress) as of this labeling review cycle dated 4/14/2020."

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 7/17/2021.

Table 3 provides Orange Book patents for the Model Labeling NDA 021135 and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
N/A						

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments: None.

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
N/A					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments: None.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
Are there changes to the manufacturer/distributor/packer statements? **YES**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review (C2)	Currently Proposed	Assessment
(b)(4)		No Change

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review (C2)	Currently Proposed	Assessment
(b)(4)		No Change

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review (C2)	Currently Proposed	Assessment
(b)(4)		(b)(4) which is satisfactory.

5. COMMENTS/CONSULTS FOR OTHER DISCIPLINES

Describe questions, issues and consults sent to and/or received from other discipline(s) (e.g., OPQ, OB, DCR):

Refer to the Consult Screening flow chart to determine any necessary consults.

(For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue). Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments: None related to the C3 Labeling Review.

Comments from C2 Labeling Review

"Questions to the chemist:
Did the firm submit **studies that support** the following found in the Prescribing Information?

Syringe Stability: Iron sucrose injection, when diluted with 0.9% NaCl at concentrations ranging from 2 mg to 10 mg of elemental iron per mL, or undiluted (20 mg elemental iron per mL) and stored in a plastic syringe, was found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C) and under refrigeration (4°C ± 2°C).

Intravenous Admixture Stability: Iron sucrose injection, when added to intravenous infusion bags (PVC or non-PVC) containing 0.9% NaCl at concentrations ranging from 1 mg to 2 mg of elemental iron per mL, has been found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C)."

- **RESPONSE**: "The firm did provide compatibility study data. Please see my assessment of the study on page 52-53 of my DP quality review. The compatibility data is adequate."

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column,

you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container (20 mg/mL)	Draft	**50 mg**: 2.5 mL SDV **100 mg**: 5 mL SDV **200 mg**: 10 mL SDV	10/31/2019	**C2: Satisfactory** **C3: Satisfactory**
Blister	NA			
Carton	Draft	**50 mg/2.5 mL** and **100 mg/5 mL**: 10- and 25-count SDVs **200 mg/10 mL**: 5- and 10-count SDVs	10/31/2019	**C2: Satisfactory** **C3: Satisfactory**
(Other – specify)	NA			
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	9/2020	12/28/2020	Revise
Medication Guide	NA			
Patient Information	NA			

Susan Rimmel

Digitally signed by Susan Rimmel
Date: 7/21/2021 04:45:39PM
GUID: 57e14a7301fe42aa569d1859f813583c

Ellen Hwang

Digitally signed by Ellen Hwang
Date: 7/22/2021 09:12:03AM
GUID: 5256bdc00002af3bc3fa942a9512a891

[redacted]

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	4/14/2020
ANDA Number(s)	212340
Review Number	2
Applicant Name	Sandoz Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Iron Sucrose Injection USP, 50 mg Elemental Iron/2.5 mL (20 mg/mL), 100 mg Elemental Iron/5 mL (20 mg/mL) and 200 mg Elemental Iron/10 mL (20 mg/mL) Single-Dose Vials
Proposed Proprietary Name	None
Submission Received Date	10/31/2019
Primary Labeling Reviewer	Jim Barlow RPh
Secondary Labeling Reviewer	Refer to signature page

Review Conclusion

☐ ACCEPTABLE – No Comments
☒ ACCEPTABLE – Include Post Approval Comments
☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant
☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Labeling

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No (If yes, indicate ANDA number)

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on (add date) based on your submission(s) received (add date):

N/A

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission (s) received 10/31/2019.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).
YES

Prescribing Information -
Please correct the revisions date to reflect the recent revisions at the end of the HIGHLIGHTS of PRESCRIBING INFORMATION and HOW SUPPLIED sections. (Revise from "04/2019" to "10/2019")

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

The below comments are from the labeling review C1 based on the submission dated 8/28/2019.

Reviewer Comments: Revised as requested by the Agency. ACCEPTABLE

1. GENERAL COMMENTS –
Please comment as to whether text appears on your cap/ferrule overseal. USP standard prohibits the use of certain statements on the cap/ferrule overseal. We refer you to the following address for additional information and guidance:
https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/genChapter1Labeling.pdf

Response 1:
Sandoz confirms that text does not appear on the cap/ferrule overseal of Iron Sucrose Injection USP, 50 mg Elemental Iron/2.5 mL (20 mg/mL), 100 mg Elemental Iron/5 mL (20 mg/mL) and 200 mg Elemental Iron/10 mL (20 mg/mL) Single-Dose Vials.

2. CONTAINERS – Revise the Principal Display Panel to read as follows to be in accordance with the reference listed drug: (Below is an example for 50 mg strength, but the same format applies to all proposed strengths).
Iron Sucrose
Injection USP
50 mg Elemental
Iron per 2.5 mL
(20 mg/mL)
FOR INTRAVENOUS USE ONLY
2.5 mL Single-Dose Vial
Discard Unused Portion Rx Only

Response 2:
Sandoz has revised the container labels as per the Agency's request. Please find enclosed in Module 1.14.1.1 the draft container labels and in Module 1.14.1.2 the comparison between the proposed and previously submitted container labels.

3. CARTONS – See comments under 2. above. Below is an example for 50 mg strength, but the same format applies to all proposed strengths/carton sizes)

Response 3:
Sandoz has revised the carton labeling as per the Agency's request. Please find enclosed in Module 1.14.1.1 the revised carton labeling. A comparison of the proposed carton labeling to the previously submitted carton labeling is provided in Module 1.14.1.2.

4. PRESCRIPTION INFORMATION
How supplied – Revise to read as follows – (Delete "FE" throughout the text)
Iron sucrose injection is supplied sterile in 2.5 mL, 5 mL, and 10 mL single-dose vials. Each 2.5 mL vial contains 50 mg elemental iron, each 5 mL vial contains 100 mg elemental iron and each 10 mL vial contains 200 mg elemental iron (20 mg/mL).
NDC 0781-3485-95 50 mg/2.5 mL Single-Dose Vial Packages of 10
NDC 0781-3485-96 50 mg/2.5 mL Single-Dose Vial Packages of 25
NDC 0781-3486-95 100 mg/5 mL Single-Dose Vial Packages of 10
NDC 0781-3486-96 100 mg/5 mL Single-Dose Vial Packages of 25
NDC 0781-3487-14 200 mg/10 mL Single-Dose Vial Packages of 5
NDC 0781-3487-92 200 mg/10 mL Single-Dose Vial Packages of 10

Response 4:
Sandoz has revised the Package Insert in accordance with the Agency's request. Please find enclosed in Module 1.14.1.3 a copy of the current labeling in both Word and PDF formats. In **addition, enclosed in Module 1.14.3.1 is the annotated labeling comparison.**

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments:
Revised as requested by the Agency. **ACCEPTABLE**

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:
None

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? NO If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? YES If Yes, please explain. Note as stated in the Policy Alert column: No Actions (AP/TA/CR) can be taken prior to contacting Policy Lead, Laura Ciurca. No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL for Bioequivalence or Quality. Issue Description: Requests FDA to require identical manufacturing process, physico-chemical properties, BE standards
Is the drug product listed on the Susceptibility Test Interpretive Criteria web page? NO

3.2 MODEL LABELING

Table 1: Review Model Labeling (Check the box used as the Model Labeling)
☒ MOST RECENTLY APPROVED NDA MODEL LABELING *(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)* **NDA#/Supplement# (S-000 if original):** 021135/35 **Supplement Approval Date:** 12/19/2018 **Proprietary Name:** Venofer® **Established Name:** Iron Sucrose Injection, USP **Description of Supplement**: This Prior Approval supplemental new drug application provides for updates to the United States Prescribing Information with the Pregnancy Lactation Labeling Rule (PLLR) content and format Requirements.
☐ MOST RECENTLY APPROVED ANDA MODEL LABELING ANDA#/Supplement# (S-000 if original): Supplement Approval Date: Proprietary Name: Established Name: Description of Supplement:
☐ TEMPLATE (e.g., BPCA, PREA, Carve-out):
☐ OTHER (Describe):

Reviewer Assessment:

Is the Prescribing Information or Drug Facts Labeling (OTC) same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old), or 201.66 (OTC)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:
ACCEPTABLE

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: **Source: SPL from AR submitted 1/7/2019**]

NDC 0517-2325-10

Venofer®

(IRON SUCROSE INJECTION, USP)

50 mg Elemental Iron per 2.5 mL (20 mg/mL)

2.5 mL Single-Use Vial
Discard Unused Portion
FOR INTRAVENOUS USE ONLY
Rx Only

Each 2.5 mL contains: 50 mg elemental iron (as iron sucrose) in water for injection. The drug product contains approximately 30% sucrose w/v (300 mg/mL). pH 10.5 to 11.1. Osmolarity 1,250 mOsmol/L. Contains no preservatives. Store at 20° to 25°C (68° to 77°F). Rev. 10/12

AMERICAN REGENT, INC.
SHIRLEY, NY 11967

Lot / Exp.

NDC 0517-2340-01

Venofer®

(IRON SUCROSE INJECTION, USP)

100 mg Elemental Iron per 5 mL (20 mg/mL)

5 mL Single-Use Vial
Discard Unused Portion
FOR INTRAVENOUS USE ONLY
Rx Only

Each 5 mL contains: 100 mg elemental iron (as iron sucrose) in water for injection. The drug product contains approximately 30% sucrose w/v (300 mg/mL). pH 10.5 to 11.1. Osmolarity 1,250 mOsmol/L. Contains no preservatives. Store at 20° to 25°C (68° to 77°F). Rev. 10/12

AMERICAN REGENT, INC.
SHIRLEY, NY 11967

Lot / Exp.

Venofer®

(IRON SUCROSE INJECTION, USP)

100 mg Elemental Iron per 5 mL (20 mg/mL)

NDC 0517-2340-25
25 x 5 mL Single-Use Vials
Discard Unused Portion

Rx Only

FOR INTRAVENOUS USE ONLY
Each 5 mL contains: 100 mg elemental iron (as iron sucrose) in water for injection. The drug product contains approximately 30% sucrose w/v (300 mg/mL). pH 10.5 to 11.1. Osmolarity 1,250 mOsmol/L. Contains no preservatives. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). Sterile.
Venofer® is manufactured under license from Vifor (International) Inc., Switzerland.

AMERICAN REGENT, INC.
SHIRLEY, NY 11967

Rev. 10/12

Lot / Exp.


Venofer®
(IRON SUCROSE INJECTION, USP)
100 mg Elemental Iron per 5 mL (20 mg/mL)
NDC 0517-2340-10
10 x 5 mL
Single-Use Vials
5 mL Single-Use Vial - Discard Unused Portion
Rx Only
FOR INTRAVENOUS USE ONLY
Each 5 mL contains: 100 mg elemental iron (as iron sucrose) in water for injection. The drug product contains approximately 30% sucrose w/v (300 mg/mL). pH 10.5 to 11.1. Osmolarity 1,250 mOsmol/L. Contains no preservatives. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). Sterile.
Rev. 10/12
AMERICAN REGENT, INC.
SHIRLEY, NY 11967
NC
0517-2340-10
Venofer® is manufactured under license from Vifor (International) Inc., Switzerland

PROPOSED labels for this drug product submitted 10/31/2019:

(b)(4)

(b)(4)

(b)(4)

(b)(4)

3.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 4/14/2020.

Table 2: United States Pharmacopeia (USP)				
	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)

Currently Official	YES	[redacted]	Iron Sucrose Injection USP	(b)(4)
Not Yet Official	N/A	N/A	N/A	N/A

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **YES**

Reviewer Comments: ACCEPTABLE

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

Is the drug product subject of a USP monograph? ☒ Yes ☐ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☒ Statement not needed

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 4/14/2020.

Table 3 provides Orange Book patents for the Model Labeling 021135 and ANDA patent certifications. (For

applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
N/A			None			N/A

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

None

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
N/A		None			N/A

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments:

None

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **YES**
Are there changes to the manufacturer/distributor/packer statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	Currently Proposed	Assessment

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
(b)(4)		NO revisions. ACCEPTABLE

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	Currently Proposed	Assessment

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products	
(b)(4)	Revised per Agency's request. ACCEPTABLE

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	Currently Proposed	Assessment

Table 7: Manufacturer/Distributor/Packer Statements	
(b)(4)	No revisions. ACCEPTABLE

5. COMMENTS/CONSULTS FOR OTHER DISCIPLINES

Describe questions, issues and consults sent to and/or received from other discipline(s) (e.g., OPQ, OB, DCR):

Refer to the Consult Screening flow chart to determine any necessary consults.

(For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue). Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments:

CHEMISTRY is INADEQAUTE-MAJOR as of this labeling review cycle dated 4/14/2020.
BIOEQUIVALENCE is INADEQUATE-MAJOR (in-progress) as of this labeling review cycle dated 4/14/2020.

Questions to the chemist:
Did the firm submit studies that support the following found in the Prescribing Information?

Syringe Stability: Iron sucrose injection, when diluted with 0.9% NaCl at concentrations ranging from 2 mg to 10 mg of elemental iron per mL, or undiluted (20 mg elemental iron per mL) and stored in a plastic syringe, was found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C) and under refrigeration (4°C ± 2°C).

Intravenous Admixture Stability: Iron sucrose injection, when added to intravenous infusion bags (PVC or non-PVC) containing 0.9% NaCl at concentrations ranging from 1 mg to 2 mg of elemental iron per mL, has been found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C).

RESPONSE –

Hi Jim,
The firm did provide compatibility study data. Please see my assessment of the study on page 52-53 of my DP quality review. The compatibility data is adequate. Thanks

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

7. FOR EACH ROW, YOU MUST CHOOSE AN ITEM "FINAL, DRAFT, OR "NA". IF YOU ENTER "NA" UNDER THE SECOND COLUMN, YOU DO NOT NEED TO ENTER "NA" FOR THE REMAINING COLUMNS.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container (50 mg and 100 mg strength vials) ONLY	Final	1s	10/31/2019	ACCEPTABLE
Carton (50 mg and 100 mg strength vials) ONLY	Final	(1 x 10) 10s and (1 x 25) 25s	10/31/2019	ACCEPTABLE
Carton (200 mg strength vials) ONLY	**Final**	(1 x 5) 5s and (1 x 10) 10s	10/31/2019	ACCEPTABLE
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	04/2019	10/31/2019	ACCEPTABLE See POST APPROVAL revisions request.
SPL Data Elements		04/2019	8/28/2019	DATA ELEMENTS are ACCEPTABLE

Ellen Hwang

Digitally signed by Ellen Hwang
Date: 4/21/2020 02:10:00PM
GUID: 5256bdc00002af3bc3fa942a9512a891

James Barlow

Digitally signed by James Barlow
Date: 4/14/2020 01:23:01PM
GUID: 508da70800028bcca2d0465dabab258f

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	9/26/2019
ANDA Number(s)	212340
Review Number	1
Applicant Name	Sandoz Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Iron Sucrose Injection USP, 50 mg Elemental Iron/2.5 mL (20 mg/mL), 100 mg Elemental Iron/5 mL (20 mg/mL) and 200 mg Elemental Iron/10 mL (20 mg/mL) Single-Dose Vials
Proposed Proprietary Name	None
Submission Received Date	8/28/2019
Primary Labeling Reviewer	Jim Barlow RPh
Secondary Labeling Reviewer	Refer to signature page

Review Conclusion

☐ ACCEPTABLE – No Comments
☐ ACCEPTABLE – Include Post Approval Comments
☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant
☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Labeling

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List	☒ Yes	☐ No
Acceptable for Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No (If yes, indicate ANDA number)

TABLE OF CONTENTS

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on 9/26/2019 based on your submission(s) received 8/28/2019:

1. **GENERAL COMMENTS** -
   Please comment as to whether text appears on your cap/ferrule overseal. USP standard prohibits the use of certain statements on the cap/ferrule overseal. We refer you to the following address for additional information and guidance:
   https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/genChapter1Labeling.pdf

2. **CONTAINERS** – Revise the Principle Display Panel to read as follows to be in accordance with the reference listed drug: (Below is an example for 50 mg strength, but the same format applies to all proposed strengths)

3. **CARTONS** - See comments under 2. above. (Below is an example for 50 mg strength, but the same format applies to all proposed strengths/carton sizes)

4. **PRESCRIBING INFORMATION** –
   How Supplied - Revise to read as follows – (Delete "FE" throughout the text)
   Iron sucrose injection is supplied sterile in 2.5 mL, 5 mL, and 10 mL single-dose vials. Each 2.5 mL vial contains 50 mg elemental iron, each 5 mL vial contains 100 mg elemental iron and each 10 mL vial contains 200 mg elemental iron (20 mg/mL).

NDC 0781-3485-95	50 mg/2.5 mL Single-Dose Vial	Packages of 10
NDC 0781-3485-96	50 mg/2.5 mL Single-Dose Vial	Packages of 25
NDC 0781-3486-95	100 mg/5 mL Single-Dose Vial	Packages of 10
NDC 0781-3486-96	100 mg/5 mL Single-Dose Vial	Packages of 25
NDC 0781-3487-14	200 mg/10 mL Single-Dose Vial	Packages of 5
NDC 0781-3487-92	200 mg/10 mL Single-Dose Vial	Packages of 10

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

N/A

1.3 POST APPROVAL REVISIONS

N/A

2. LABELING REVIEW INFORMATION

2.1 REGULATORY INFORMATION

Are there any applicable issues in DLR's SharePoint Drug Facts? NO If YES, please explain.
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? YES If YES, please explain. Note as stated in the Policy Alert column: No Actions (AP/TA/CR) can be taken prior to contacting Policy Lead, Laura Ciurca. No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL for Bioequivalence or Quality. Issue Description: Requests FDA to require identical manufacturing process, physico-chemical properties, BE standards
Is the drug product listed in the Susceptibility Test Interpretive Criteria web page? NO
Is there a mid-review cycle meeting (MRCM) task in Platform? NO If **YES**, what is the proposed agenda from DLR for MRCM?

N/A

Is there a Product Development or Pre-ANDA Submission Project under the ANDA Program? NO

If **YES**, review the meeting minutes and state the labeling impact, if any.

N/A

2.2 MODEL LABELING

2.2.1 MODEL PRESCRIBING INFORMATION/DRUG FACTS LABELING (OTC)

Table 1: Review Model Labeling for Prescribing Information, Patient Labeling, or Drug Facts Labeling (OTC) (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)* **NDA#/Supplement# (S-000 if original):** 021135/35 **Supplement Approval Date:** 12/19/2018 **Proprietary Name:** Venofer® **Established Name:** Iron Sucrose Injection, USP **Description of Supplement**: This Prior Approval supplemental new drug application provides for updates to the United States Prescribing Information with the Pregnancy Lactation Labeling Rule (PLLR) content and format Requirements.
☐ MOST RECENTLY APPROVED ANDA MODEL LABELING ANDA#/Supplement# (S-000 if original): Supplement Approval Date: Proprietary Name: Established Name: Description of Supplement:
☐ TEMPLATE (e.g., BPCA, PREA, Carve-out):
☐ OTHER (Describe): ANDA 210103 also utilized for consistency in labeling

2.2.2 MODEL CONTAINER LABELS

Model container/carton/blister labels (Source: SPL from AR submitted 1/7/2019)


NDC 0517-2325-10
Venofer®
(IRON SUCROSE INJECTION, USP)
50 mg Elemental Iron per 2.5 mL (20 mg/mL)
2.5 mL Single-Use Vial
Discard Unused Portion
FOR INTRAVENOUS USE ONLY
Rx Only
Each 2.5 mL contains: 50 mg elemental iron (as iron sucrose) in water for injection. The drug product contains approximately 30% sucrose w/v (300 mg/mL). pH 10.5 to 11.1. Osmolarity 1,250 mOsmol/L. Contains no preservatives. Store at 20° to 25°C (68° to 77°F). Rev. 10/12
AMERICAN REGENT, INC.
SHIRLEY, NY 11967
Lot / Exp.
NDC 0517-2340-01
Venofer®
(IRON SUCROSE INJECTION, USP)
100 mg Elemental Iron per 5 mL (20 mg/mL)
5 mL Single-Use Vial
Discard Unused Portion
FOR INTRAVENOUS USE ONLY
Rx Only
Each 5 mL contains: 100 mg elemental iron (as iron sucrose) in water for injection. The drug product contains approximately 30% sucrose w/v (300 mg/mL). pH 10.5 to 11.1. Osmolarity 1,250 mOsmol/L. Contains no preservatives. Store at 20° to 25°C (68° to 77°F). Rev. 10/12
AMERICAN REGENT, INC.
SHIRLEY, NY 11967
Lot / Exp.


Venofer®
(IRON SUCROSE INJECTION, USP)
100 mg Elemental Iron per 5 mL (20 mg/mL)
NDC 0517-2340-25
25 x 5 mL Single-Use Vials
Discard Unused Portion
Rx Only
Lot / Exp.
FOR INTRAVENOUS USE ONLY
Each 5 mL contains: 100 mg elemental iron (as iron sucrose) in water for injection.
The drug product contains approximately 30% sucrose w/v (300 mg/mL). pH 10.5 to 11.1.
Osmolarity 1,250 mOsmol/L. Contains no preservatives. Store at 20° to 25°C (68° to 77°F);
excursions permitted to 15° to 30°C (59° to 86°F). Sterile.
Venofer® is manufactured under license from Vifor (International) Inc., Switzerland.
AMERICAN REGENT, INC.
SHIRLEY, NY 11967
Rev. 10/12


Venofer®
(IRON SUCROSE INJECTION, USP)
100 mg Elemental Iron per 5 mL (20 mg/mL)
NDC 0517-2340-10
10 x 5 mL
Single-Use Vials
5 mL Single-Use Vial - Discard Unused Portion
Rx Only
FOR INTRAVENOUS USE ONLY
Each 5 mL contains: 100 mg elemental iron (as iron sucrose) in water for injection. The drug product contains approximately 30% sucrose w/v (300 mg/mL). pH 10.5 to 11.1. Osmolarity 1,250 mOsmol/L. Contains no preservatives. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). Sterile.
Rev. 10/12
AMERICAN REGENT, INC.
SHIRLEY, NY 11967
NC
0517-2340-10
Venofer® is manufactured under license from Vifor (International) Inc., Switzerland

PROPOSED labels for this ANDA

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

2.3 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 9/26/2019.

Table 2: USP				
	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)

Currently Official	YES	[redacted]	Iron Sucrose Injection USP	(b)(4)
Not Yet Official	N/A	N/A	N/A	N/A

2.4 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 9/26/2019.

Table 3 provides Orange Book patents for the Model Labeling (021135) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 3: Impact of Model Labeling Patents on ANDA Labeling

Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
N/A			None			N/A

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
N/A		None			N/A

2.5 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER

Table 5: Comparison of Manufacturer/Distributor/Packer Labeling Statements

Name and Address of ANDA Manufacturer/Distributor/Packer (cite source as applicable)	Name and Address on ANDA Container/Carton	Name and Address on ANDA Prescribing Information

Drug Substance (API) Manufacturer Name(s)	Location of API Manufacturing Facility
(b)(4)	

(b)(4)

3. ASSESSMENT OF ANDA LABELING AND LABELS

Is this product Rx or OTC? Please check one.

☒ Rx Product (If Rx, skip 3.2 OTC DRUG PRODUCT.)
☐ OTC Product (If OTC, skip 3.1 RX DRUG PRODUCT.)

3.1 RX (PRESCRIPTION) DRUG PRODUCT

3.1.1 RX: PRESCRIBING INFORMATION

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **NO**
Is the established name the same as the USP monograph title appearing in section 2.3? **YES**
Is the established name the same as the RLD's nonproprietary name? **YES**
If NO is answered to EITHER of the 2 questions above, then advise firm to revise to the USP name (if applicable) and include justification language under Reviewer Comments.
Does the Model Labeling have combined insert labeling for multiple NDAs or dosage forms? **NO**
Is the applicant's "patent carve out" acceptable? **NA**
Is the applicant's "exclusivity carve out" acceptable? **NA**
Is the Manufacturer/Distributor/Packer statement acceptable? **YES**
Is there a Pregnancy Registry for the NDA RLD? **NO** (If YES, determine if it is required for the ANDA and provide assessment under Reviewer Comments.)
For antiretroviral applications, did the applicant state its intent to join the Antiretroviral Pregnancy Registry (APR) upon full approval? **NO**

Reviewer Comments:
See deficiencies above.

3.1.1.1 RX: DESCRIPTION

Table 6: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	Each mL contains 20 mg elemental iron as iron sucrose in water for injection. Venofer is available in 10 mL single-dose vials (200 mg elemental iron per 10 mL), 5 mL single-dose vials (100 mg elemental iron per 5 mL), and 2.5 mL single-dose vials (50 mg elemental iron per 2.5 mL). The drug product contains approximately 30% sucrose w/v (300 mg/mL) and has a pH of 10.5 to 11.1. The product contains no preservatives. The osmolarity of the injection is 1,250 mOsmol/L.

Table 6: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
ANDA Labeling	(b)(4)

Reviewer Assessment:

Are the inactive ingredients accurate? **PENDING DRUG PRODUCT REVIEW**
For products required to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **NA**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **NO**
Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling? **PENDING**
If the labeling includes a "Does not contain…" statement, is it acceptable/allowed? **NA** Has the statement been verified by drug product reviewer? **NA**

Reviewer Comments:
CHEMISTRY is pending as of this labeling review cycle dated 9/26/2019.

3.1.1.2 RX: HOW SUPPLIED/STORAGE AND HANDLING

Table 7: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	Venofer is supplied sterile in 10 mL, 5 mL, and 2.5 mL single-dose vials. Each 10 mL vial contains 200 mg elemental iron, each 5 mL vial contains 100 mg elemental iron, and each 2.5 mL vial contains 50 mg elemental iron (20 mg/mL). NDC-0517-2310-05 200 mg/10 mL Single-Dose Vial Packages of 5 NDC-0517-2310-10 200 mg/10 mL Single-Dose Vial Packages of 10 NDC-0517-2340-01 100 mg/5 mL Single-Dose Vial Individually Boxed NDC-0517-2340-10 100 mg/5 mL Single-Dose Vial Packages of 10 NDC-0517-2340-25 100 mg/5 mL Single-Dose Vial Packages of 25 NDC-0517-2340-99 100 mg/5 mL Single-Dose Vial Packages of 10 NDC-0517-2325-10 50 mg/2.5 mL Single-Dose Vial Packages of 10 NDC-0517-2325-25 50 mg/2.5 mL Single-Dose Vial Packages of 25 **16.2 Stability and Storage** Contains no preservatives. Store in original carton at 20° to 25°C (68° to 77° F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not freeze. *Syringe Stability*: Venofer, when diluted with 0.9% NaCl at concentrations ranging from 2 mg to 10 mg of elemental iron per mL, or undiluted (20 mg elemental iron per mL) and stored in a plastic syringe, was found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C) and under refrigeration (4°C ± 2°C). *Intravenous Admixture Stability:* Venofer, when added to intravenous infusion bags (PVC or non-PVC) containing 0.9% NaCl at concentrations ranging from 1 mg to 2 mg of elemental iron per mL, has been found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C). Do not dilute to concentrations below 1 mg/mL. Do not mix Venofer with other medications or add to parenteral nutrition solutions for intravenous infusion. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to infusion.

Table 7: Comparison of Model Labeling to ANDA Labeling	
ANDA Labeling	(b)(4)

Reviewer Assessment:

Are all of the submitted labels and labeling consistent with the How Supplied section? **YES**
Is the description (e.g., scoring, color, imprint) of the finished product in the HOW SUPPLIED section accurate? **PENDING DRUG PRODUCT REVIEW**
Does the ANDA require the same color coding as the Model? **NO**
Is there any difference in scoring configuration between the ANDA and the Model Labeling? **NA**
Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **YES**
If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **NA**
Is the storage or dispensing statement acceptable as compared to the Model Labeling? **YES**
Is the storage or dispensing statement acceptable as compared to the USP? **YES**

Reviewer Comments: See deficiencies above.
CHEMISTRY is pending as of this labeling review cycle dated 9/26/2019.

3.1.2 RX: MEDICATION GUIDE

Is Medication Guide required? **CLICK HERE**
If YES go to Reviewer Assessment below, if NO go to section 3.1.3.

Reviewer Assessment:

Was Medication Guide submitted? **CLICK HERE**
Is the Medication Guide same as the model labeling, except for allowable differences? **CLICK HERE**

Has the Applicant committed to provide a sufficient number of medication guides? **CLICK HERE**
Is the phonetic spelling of the proprietary or established name present? **CLICK HERE**
Is FDA 1-800-FDA-1088 phone number included? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.3 RX: OTHER PATIENT LABELING

Are other patient labeling required? **CLICK HERE**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.

Reviewer Assessment:

Was other patient labeling submitted? **CLICK HERE**
Is the patient labeling the same as the model labeling, except for allowable differences? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.4 RX: CONTAINER LABEL

Was container label (other than Blisters) submitted? **YES**
(For BLISTER labels go to section 3.1.5.)

Reviewer Assessment:

Is the established name acceptable? **YES**
Is title case used in expressing the established name? **YES**
Does labeling comply with Tall Man lettering recommendations found on FDA webpage? **NA**
If the container label is too small to contain all required information, does it meet the "too small" exemption found in 21 CFR 201.10(i)? **NA**
Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **YES**
Is the following information properly displayed?
- Net quantity statement: **YES**
- Route(s) of administration (other than oral): **NO**
- Warnings (if any) or cautionary statements (if any): **NA**
- Medication Guide Pharmacist instructions per 21 CFR 208.24(d)**:** **NA**
- Controlled substance symbol: **NA**
- Usual Dosage statement: **YES**
- Product strength equivalency statement: **YES**
- NDC: **YES**
- Bar code per 21 CFR 201.25(c)(2): **YES**

Is the Manufacturer/Distributor/Packager statement acceptable? **YES**
Are the USP recommendations and/or differences in test methods (e.g., organic impurities, assay) reflected on the label(s)? **PENDING**
Is the storage or dispensing statement consistent with the How Supplied section of the insert? **YES**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **NO**
Are multiple strengths differentiated by use of different color or other acceptable means? **YES**
Are the labels of related products differentiated to avoid selection errors? **YES**
Does the ANDA require the same color coding as the Model? **NO**
Are requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100)? **YES**

Reviewer Comments:
See deficiencies above.

3.1.4.1 RX: CONTAINER LABEL FOR PARENTERAL SOLUTIONS

Is container for parenteral solution? **YES**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.2.

Reviewer Assessment:

Is the product strength expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP General Chapter <7> Labeling **YES**
If volume is less than 1 mL, is strength per fraction of a milliliter the only expression of strength? **NA**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **YES**

Reviewer Comments:
ACCEPTABLE

3.1.4.2 RX: CONTAINER LABEL FOR SOLID INJECTABLE

Is container for solid injectable (other than Pharmacy Bulk Package)? **CLICK HERE**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.3.

Reviewer Assessment:

Is the strength in terms of the total amount of drug per vial? **CLICK HERE**
Are instructions for reconstitution and resultant concentration provided, if space permits? **CLICK HERE**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.4.3 RX: CONTAINER LABEL FOR PHARMACY BULK PACKAGE

Is container a Pharmacy Bulk Package (parenteral preparations for admixtures)? **CLICK HERE**
If YES go to Reviewer Assessment below, if NO go to section 3.1.5.

Reviewer Assessment:

Is the strength in terms of the total amount of drug per vial? **CLICK HERE**
Is there a prominent, boxed declaration reading "Pharmacy Bulk Package – Not for Direct Infusion" on the principal display panel following the expression of strength? **CLICK HERE**
Does the container label include graduation marks? **CLICK HERE**
Are instructions for reconstitution and resultant concentration provided, if space permits? **CLICK HERE**
Does label contain the required information on proper aseptic technique including time frame in which the container may be used once it has been entered? **CLICK HERE**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.5 RX: UNIT DOSE BLISTER LABEL

Is container a Unit Dose Blister Pack? **CLICK HERE**
If YES go to Reviewer Assessment below, if NO go to section 3.1.6.

Reviewer Assessment:

Does each blister include only one dosage unit (e.g., one tablet, one capsule)? **CLICK HERE**

Do proprietary name, established name, strength, bar code, and manufacturer/distributor/packer appear accurately on each blister cell? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.6 RX: CARTON (OUTER OR SECONDARY PACKAGING) LABELING

Was carton labeling submitted? **YES**
If YES go to Reviewer Assessment below, if NO go to section 3.3.

Reviewer Assessment:

Are the answers to the Container Label questions the same for the Carton Labeling? **YES** If no, please explain the differences in the Reviewer Comments section.
If container is too small or otherwise unable to accommodate a label with enough space to include all required information, is all required information present on the carton labeling? **YES**

Reviewer Comments:
See deficiencies above.

3.2 OTC (OVER THE COUNTER) DRUG PRODUCT

3.2.1 OTC: LABELING THAT INCLUDES DRUGS FACTS INFORMATION

Reviewer Assessment:

Is Drug Facts Labeling format acceptable per 21 CFR 201.66? **CLICK HERE**
Does "Questions?" have a toll-free number no less than 6 pt. font size per 21 CFR 201.66(c)(9) or "1-800-FDA-1088" per 21 CFR 201.66 (c)(5)(vii)? **CLICK HERE**
Did firm submit a Labeling Format Information Table to evaluate the font size? **CLICK HERE**
Is the applicant's "patent carve out" acceptable? **CLICK HERE**
Is the applicant's "exclusivity carve out" acceptable? **CLICK HERE**
Is the established name for this ANDA acceptable? **CLICK HERE**
Is title case used in expressing the established name? **CLICK HERE**
Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **CLICK HERE**
Is the following information properly displayed?
- Pharmacological category: **CLICK HERE**
- Net quantity statement: **CLICK HERE**
- Route(s) of administration (other than oral): **CLICK HERE**
- Warnings (if any) or cautionary statements (if any): **CLICK HERE**
- NDC: **CLICK HERE**
- Bar code per 21 CFR 201.25(c)(2): **CLICK HERE**

Is the Manufacturer/Distributor/Packager statement acceptable? **CLICK HERE**
Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling? **CLICK HERE**
Is the storage statement acceptable? **CLICK HERE**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **CLICK HERE**
Are multiple strengths differentiated by use of different color or other acceptable means? **CLICK HERE**
Are the labels of related products differentiated to avoid selection errors? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.2.1.1 OTC: INACTIVE INGREDIENTS COMPARISON

Table 8: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	Click here to enter text.
ANDA Labeling	Click here to enter text.

Reviewer Assessment:

Are the inactive ingredients accurate? **CLICK HERE**
Are the inactive ingredients listed in alphabetical order? **CLICK HERE**
For products required/recommended to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **CLICK HERE**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **CLICK HERE**
If the labeling includes a "Does not contain…" statement, is it acceptable/allowed? **CLICK HERE** Has the statement been verified by drug product reviewer? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.2.1.2 OTC: HOW SUPPLIED AND STORAGE INFORMATION

Table 9: Comparison of Model Labeling to ANDA finished product	
Model Labeling	**Description of Finished Product** (Source: Click here to enter text.) Click here to enter text. **Package Configurations** (Source: Click here to enter text.) Click here to enter text. **Storage Conditions** (Source: Click here to enter text.) Click here to enter text.
ANDA	**Description of Finished Product** (Source: Click here to enter text.) Click here to enter text. **Package Configurations** (Source: Click here to enter text.) Click here to enter text. **Storage Conditions** (Source: Click here to enter text.) Click here to enter text.

Reviewer Assessment:

Is the description (scoring, color and imprint) of the finished product consistent with the Drug Product Quality submission? **CLICK HERE**
Is there any difference in scoring configuration between the ANDA and the Model Labeling? **CLICK HERE**
Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **CLICK HERE**
If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **CLICK HERE**
Is the storage statement acceptable as compared to the Model Labeling? **CLICK HERE**
Is the storage statement acceptable as compared to USP? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.2.2 OTC: PATIENT LABELING

Is patient labeling required? **CLICK HERE**
If YES go to Reviewer Assessment below, if NO go to section 3.3.

Reviewer Assessment:

Was patient labeling submitted? **CLICK HERE**
Is the patient labeling the same as the model labeling, except for allowable differences? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.3 CONTAINER/CLOSURE

Reviewer Assessment:

Describe container closure (e.g., 30s CRC, 100s non-CRC) and cite source of information in **Reviewer Comments** text box.
Is the use of a child-resistant closure (CRC) or non-CRC appropriate? **NA**
Are the tamper evident requirements met for OTC, Ophthalmic and Controlled Substances **NA**

For ophthalmic products:
Does this ophthalmic product cap color match the American Academy of Ophthalmology (AAO) packaging color-coding scheme? **NA**

For parenteral products:
Is there text on the cap/ferrule overseal of this injectable product? **APPLICANT DID NOT PROVIDE INFORMATION**
If YES, does text comply with the recommendations in USP General Chapter <7> Labeling? **NA**
What is the cap color? **Green for the 50 mg vial and Purple for the 100 mg and 200 mg strength vial**
NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.

Reviewer Comments: CHEMISTRY pending as of tis labeling review dated 9/26/2019.
Will ask the firm to confirm that there is NO text on the cap overseal. See deficiencies above.

Exhibit/ANDA Lots:

(b)(4)

3.4 CALCULATIONS FOR CONTENTS AND/OR VERIFICATION OF ALUMINUM CONTENT

Is the calculation of any content(s) [e.g., phenylalanine] or verification of aluminum content required? **CLICK HERE**

Table 10: Ingredients		
Ingredient	**Stated Content**	**Location of the Information**
Click here to enter text.	Click here to enter text.	Click here to enter text.

Reviewer Assessment:

Are the stated contents in the table above acceptable? **CLICK HERE**
Aluminum content in small volume parenterals, large volume parenterals, and pharmacy bulk packages, which are used in TPNs, need to be in the labeling per 21 CFR 201.323.
Did the drug product reviewer verify the aluminum content? **CLICK HERE**
Are the labeling requirements met per 21 CFR 201.323? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.5 STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS

Was SPL submitted? **YES**

Table 11: ANDA Tablet/Capsule Size and Imprint		
Tablet/Capsule Strength	**ANDA Tablet/Capsule Size (mm) and imprint code from SPL**	**ANDA Tablet/Capsule Size (mm) and imprint code (Cite source: e.g., Drug Product Review, Product Specification in 3.2.P.5.1, and Commercial Batch Record in 3.2.P.3.3)**
N/A	None	N/A

Reviewer Assessment:

Are the data elements (strength, inactive ingredients, product characteristics, packaging etc.) consistent with the information submitted in the ANDA labeling? **YES**

Reviewer Comments:
Appears to be ACCEPTABLE, however, CHEMISTRY is pending as of this labeling review cycle dated 9/26/2019.

4. COMMENTS/CONSULTS FOR OTHER DISCIPLINES

Describe questions, issues, and consults sent to and/or received from other discipline(s) (e.g., OPQ, OB, DCR).

Refer to the Consult Screening flow chart to determine any necessary consults.

(For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue.)

Reviewer Comments:
CHEMISTRY and BIOEQUIVALENCE are pending as of this labeling review cycle dated 9/26/2019.

Questions to the chemist:
Did the firm submit studies that support the following found in the Prescribing Information?

Syringe Stability: Iron sucrose injection, when diluted with 0.9% NaCl at concentrations ranging from 2 mg to 10 mg of elemental iron per mL, or undiluted (20 mg elemental iron per mL) and stored in a plastic syringe, was found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C) and under refrigeration (4°C ± 2°C).

Intravenous Admixture Stability: Iron sucrose injection, when added to intravenous infusion bags (PVC or non-PVC) containing 0.9% NaCl at concentrations ranging from 1 mg to 2 mg of elemental iron per mL, has been found to be physically and chemically stable for 7 days at controlled room temperature (25°C ± 2°C).

RESPONSE - Pending

5. SPECIAL CONSIDERATIONS

None

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Table 12: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container (50 mg, 100 mg and 200 mg strength vials)	Final	1s	8/28/2019	**Revise**
Carton (50 mg and 100 mg strength vials) ONLY	Final	(1 x 10) 10s and (1 x 25) 25s	8/28/2019	**Revise**
Carton (200 mg strength vials) ONLY	**Final**	(1 x 5) 5s and (1 x 10) 10s	8/28/2019	**Revise**
Table 13 Review Summary of Prescribing Information and Patient Labeling				

	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Draft	04/2019	8/28/2019	**Revise**
SPL Data Elements		04/2019	8/28/2019	DATA ELEMENTS are ACCEPTABLE

Ellen Hwang

Digitally signed by Ellen Hwang
Date: 10/08/2019 12:30:45PM
GUID: 5256bdc00002af3bc3fa942a9512a891

James Barlow

Digitally signed by James Barlow
Date: 10/08/2019 09:32:02AM
GUID: 508da70800028bcca2d0465dabab258f

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 212340

CHEMISTRY REVIEW(s)

ANDA Executive Summary

1. Application/Product Information

ANDA Number.	212340
Review Cycle #	3
Applicant Name	Sandoz Inc.
Drug Product Name	Iron Sucrose
Dosage Form. (click (+) for more than one)	Injection
Proposed Strength(s)	50 mg/2.5 mL, 100 mg/5 mL, 200 mg/10 mL
Route of Administration (click (+) for more than one)	Intravenous
Maximum Daily Dose	500 mg Fe, 8500 mg sucrose
Rx/OTC Dispensed	Rx
Proposed Indication	Iron sucrose injection is indicated for the treatment of iron deficiency anemia (IDA) in patients with chronic kidney disease (CKD).
Drug Product Description	Iron sucrose injection, USP, an iron replacement product, is a brown, sterile, aqueous, complex of polynuclear iron (III)-hydroxide in sucrose for intravenous use. Iron sucrose injection has a molecular weight of approximately 34,000 to 60,000 daltons and a proposed structural formula: $[Na_2Fe_5O_8(OH) \cdot 3(H_2O)]_n \cdot m(C_{12}H_{22}O_{11})$ where: n is the degree of iron polymerization and m is the number of sucrose molecules associated with the iron (III)-hydroxide. Each mL contains 20 mg elemental iron as iron sucrose in water for injection. Iron sucrose injection is available in 10 mL single-dose vials (200 mg elemental iron per 10 mL), 5 mL single-dose vials (100 mg elemental iron per 5 mL), and 2.5 mL single-dose vials (50 mg elemental iron per 2.5 mL). The drug product contains approximately 30% sucrose w/v (300 mg/mL) and has a pH of 10.5 to 11.1. The product contains no preservatives. The osmolarity of the injection is 1,250 mOsmol/L.

Co-packaged product information	N/A		
Device information, if any:	N/A		
Storage Temperature/ Conditions	Store in original carton at 20°C to 25°C (68° F to 77° F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not freeze.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Keduo Qian	Brian Connell
	Drug Product/ Labeling	Vasiliy Korotchenko	Dahui Liu
	Manufacturing	Allison Aldridge	Rose Xu
	Biopharmaceutics	N/A	N/A
	Microbiology	Andrew Brown	Denise Miller
	Other (specify):	N/A	N/A
	RBPM	Charmaine Flotildes	
	ATL	Dahui Liu	
Consults	**Discipline Consulted**	**Recommendation**	**Date**
	N/A		

2. Submission Document(s) Reviewed

Submission(s) Assessed	Document Date	Discipline(s) Affected
Resubmission/After Action- Complete; Quality/Quality Information; Quality/Microbiology Information	12/28/2020	All

Quality/Response To Information Request	12/07/2021	Drug Product, Manufacturing
Quality/Response To Information Request	04/22/2022	Drug Product, Manufacturing
Quality/Response To Information Request	07/06/2022	Drug Product, Manufacturing
Resubmission/After Action- Complete	08/18/2023	Drug Product
Response to Information Request	06/09/2025	Drug product, labeling
Response to Information Request	06/11/2025	Drug product, labeling
Response to Information Request	6/17/2025	Labeling
Previous Submission(s) Assessed	**Document Date**	**Discipline(s) Affected**
Original/Initial Submission (0001)	08/28/2019	All
Labeling/Response to Discipline Review Letter*	10/31/2019	Labeling
Bioequivalence/Response to Discipline Review Letter	04/16/2020	Drug Product
Quality/Response To Information Request	04/24/2020	Drug Product
Quality/Response to Discipline Review Letter	06/04/2020	Drug Product
* Scanned for quality information		

3. Related/Supporting Documents

a. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/ Comments
(b) (4)	II	(b) (4)	Iron Sucrose (b) (4) (b) (4)	Adequate	03/11/2024	R03 by Keduo Qian
	III			N/A		
	III			N/A		
	V			Adequate	01/06/2020	Review D018370M16 R01 by Valerie Huse
	III			N/A		

b. Other Documents: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description

NDA	N021135	RLD: Venofer® (Iron sucrose Injection, USP) by Luitpold Pharmaceuticals Inc. approved 20-MAR-2005.

4. Final Overall recommendation – Approval

Deficiencies (if applicable):

Overall Quality Deficiencies - Optional *(Deficiencies that affect multiple sub-disciplines; for subheadings use the format shown, for all deficiencies.)*

None

Drug Substance Deficiencies

None

Drug Product Deficiencies

None

Labeling Deficiencies *(Please contact OGD if you identify any Labeling deficiencies with your comments)*

None

Manufacturing Deficiencies

a. **Process:** None

b. **Facility:** None

Biopharmaceutics Deficiencies

N/A

Microbiology Deficiencies

None

Other Deficiencies *(Specify discipline, such as Environmental. For consults such as Biostatistics, PharmTox, CDRH, Clinical, etc., include consult type and specify Quality discipline – example:* ***Pharm/Tox consult for Drug Product****)*

None

Additional Comments:

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment(s) in your response: None

5. Basis for Recommendation

a. Summary of Rationale for Recommendation:

The application is approvable from CMC perspectives. The provided information for drug substance, drug product, manufacturing process, facility, and microbiology is adequate. The referenced DMF (b) (4) is adequate. The stability data support the proposed 24 months shelf life. The provided comparative characterization data is adequate. The drug product is not impacted by NDSRIs.

b. Recommendation by Subdiscipline:

Drug Substance: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

Drug Product: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

Quality Labeling: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

Manufacturing: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

Biopharmaceutics: N/A

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

Microbiology: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

Environmental: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

6. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments: None

Comparability Protocols (PACMP): No
Comments: None

Additional Comments: [redacted (b) (4)]. The PSG of this product has recommendations for comparative characterizations (both test product and RLD), which are conducted using three batches of test products manufactured using [redacted (b) (4)] Please refer to the PSG on recommendations on scale of batches used for comparative physicochemical characterizations, in vitro and in vivo BE studies.

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CHAPTER I: DRUG SUBSTANCE

IQA ANDA Assessment Guide Reference

Drug Substance Name	Iron (III) Hydroxide Sucrose Complex
ANDA Number	212340
Applicant Name	Sandoz Inc.
Assessment Cycle Number	3
DMF Number (If Applicable)	(b) (4)
DMF Status	Adequate
DMF Holder	(b) (4)

Assessment Recommendation: **Adequate**

Theme: N/A

Assessment Summary :

(b) (4). There is no monograph exists. The referenced DMF (b) (4) is assessed as Adequate per (b) (4).

See Assessment summary of the Drug Product section for citizen petition history and definition of active ingredient.

List Submissions being assessed (*Table*):

Document(s) Assessed	Date Received
Review #1	
Original submission, seq.#0001	8/28/2019
Amendment, seq. # 0002	10/31/2019
Review #2	
Amendment, Seq. #0009, response to CRL	12/28/2020
Amendment, Seq. #0010, response to IR	12/7/2021
Amendment, Seq. #0011, response to IR	4/22/2022
Amendment, Seq. #0012, response to process IR	7/6/2022
Review #3	

Multiple Categories / Subcategories, Sequence #13 (0013)	08-18-2023

Highlight Key Issues from Last Cycle and Their Resolution: DMF was inadequate in the previous cycle. Currently DMF is assessed as Adequate

Concise Description of Outstanding Issues: NONE

Select Number of Approved Comparability Protocols: 0

S.1 GENERAL INFORMATION

Generic Name	Iron Sucrose
Chemical Name(s)	Iron Sucrose – Iron Saccharate – Sucrose, Iron complex
Other Name(s)	Iron (III) – hydroxide sucrose complex
CAS Number	8047-67-4
Structure	Not Known Structure
Molecular Formula	$[Na_2Fe_5O_8 (OH)\cdot 3(H_20)]_n . m(C_{12}H_{22}O_{11})$
Molecular Weight	34000 – 60000 Da

Physical Appearance[1]	Homogenous brown-dark powder; Hygroscopic

(b) (4)

[redacted]

Assessment (Review #3): *Adequate*

Assessment in Reviews 1, 2

(b) (4)

[redacted]

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No update in Chemistry Review #3.

R REGIONAL INFORMATION

Comparability Protocols: None

Assessment: N/A

Lifecycle Management Considerations

N/A

DRUG SUBSTANCE LIST OF DEFICIENCIES: NONE

Primary Drug Substance Assessor Name and Date: Dahui Liu, Ph.D. 1/30/2020 (Review 1), 7/19/2021 (Review #2), 2/3/2022 (Review #2a), 11/02/2022 (Review #2b); Vasily Korotchenko, Ph.D., March 12, 2024 (Review #3), 07/10/2025 (Review #3a).

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

Yiwei Li, Ph. D., OLDP/DLBPI/Branch II, (CR1) 02/12/2020, Shin Grace Chou 03/01/2022 (Review 2a), Cameron Smith (Review #2b), Dahui Liu, 3/12/2024 (Review #3), 07/10/2025 (Review #3a).

CHAPTER II: DRUG PRODUCT

IQA ANDA Assessment Guide Reference

Product Information	Iron Sucrose Injection, USP an iron replacement product, is a brown, sterile, aqueous solution, complex of polynuclear iron (III)-hydroxide in sucrose for intravenous use. Iron Sucrose Injection, USP has a molecular weight of approximately 34,000 to 60,000 Daltons and a proposed structural formula: $[Na_2Fe_5O_8(OH) \cdot 3(H_2O)]_n \cdot m(C_{12}H_{22}O_{11})$ where: n is the degree of iron polymerization and m is the number of sucrose molecules associated with the iron (III)-hydroxide. Each mL contains 20 mg elemental iron as iron sucrose in water for injection. Iron sucrose injection is available in 10 mL single-dose vials (200 mg elemental iron per 10 mL), 5 mL single-dose vials (100 mg elemental iron per 5 mL), and 2.5 mL single-dose vials (50 mg elemental iron per 2.5 mL). The drug product contains approximately 30% sucrose w/v (300 mg/mL) and has a pH of 10.5 to 11.1. The product contains no preservatives. The osmolarity of the injection is 1,250 mOsmol/L. The drug product is supplied sterile in 10 mL, 5 mL, and 2.5 mL single-dose vials. Each 10 mL vial contains 200 mg elemental iron, each 5 mL vial contains 100 mg elemental iron, and each 2.5 mL vial contains 50 mg elemental iron. Store in original carton at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). [see USP Controlled Room Temperature]. Do not freeze. There is USP monograph exists for the drug product.
ANDA Number	212340
Assessment Cycle Number	3a

Drug Product (DP) Name / Strength	Iron Sucrose Injection USP, 50 mg/2.5 mL, 100 mg/5 mL and 200 mg/10 mL
Route of Administration	Intravenous
Drug Product Manufacturer	Sandoz Inc..
RLD/RS Information (Brand Name of Product, Applicant)	Venofer/ LUITPOLD PHARMACEUTICALS INC
RLD/RS Number	NDA # 021135
Proposed Indication	Iron Sucrose Injection is indicated for the treatment of iron deficiency anemia in patients with chronic kidney disease (CKD)

Assessment Recommendation: **Adequate**

Theme: N/A

Assessment Summary:
The drug product is a USP item. The firm provided 24 months long term and 12 months intermediate stability data. All data meet the specification. No significant trend is observed at long term or intermediate conditions.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Review #1	
Original submission (Seq. # 0001)	08/28/2019
Amendment (Seq. # 0002), labeling	10/31/2019
Amendment (Seq. #0007), CCS sample shipment	4/24/2020
Review #2	
Amendment, (Seq. #0009), response to CRL	12/28/2020
Amendment, (Seq. #0010), response to IR	12/07/2021
Amendment, Seq. #0011, response to IR	4/22/2022
Amendment, Seq. #0012, response to IR	7/6/2022
Review #3 and 3a	
Multiple Categories / Subcategories, Sequence #13 (0013)	08-18-2023
Sequence #0017, response to IR	6/9/2025
Sequence #0018, response to IR	6/11/2025

Sequence #0019, response to IR	6/17/2025

Highlight Key Issues from Last Cycle and Their Resolution: Gross content specification is added, as requested.

Concise Description of Outstanding Issues (*List Bullet Points with Key Information and Update as Needed*): NONE

Select Number of Approved Comparability Protocols: 0

List Current Quality Endorsement Status:

- *USP monograph for Drug Product and compliance (current USP) – status: Adequate*
- *Dissolution status: N/A*
- *Elemental impurity compliance with ICH Q3D – status: Adequate*
- *Number of Comparability protocols included: 0*

Citizen Petition (CP) History

"Response Letter From FDA CDER to Foley Hoag LLP" was published on 5/26/2021 in response to citizen petition # FDA-2016-P-1163 regarding Velphoro, submitted on 4/19/2016. In the letter, the agency stated its conclusion that the active ingredient for Venofer is ferric oxyhydroxide.

On August 3, 2021, Vifor (International) Inc., Switzerland (Vifor) submitted a Citizen Petition and Petition for Stay (Vifor Petition) (FDA-2021-P-0893) requesting the Agency reverse certain actions announced in its Velphoro Citizen Petition response.

On July 1, 2024, the Agency published a memorandum stating that the Center for Drug Evaluation and Research (CDER) "is reevaluating its determination that the active ingredient of the iron products subject to the May 26, 2021, Citizen Petition response is ferric oxyhydroxide." The memorandum also stated that during the reevaluation period, "CDER is accepting the active ingredient names as approved prior to the May 26, 2021, Citizen Petition response for all iron products subject to the May 26, 2021, Citizen Petition response..." (See Docket Nos FDA-2016-P-1163 and FDA-2021-P-0893, available at regulations.gov.)

Active ingredient definition:

Based on further internal discussions and consideration of certain issues implicated by the above petitions,the Agency has now determined that the active ingredient in Venofer is iron sucrose, and that the active moiety is ferric oxyhydroxide.

Sodium Chloride (NaCl):

Upon further evaluation of the RLD Drug Substance components, it is OPQ's current understanding that NaCl is an excipient in the RLD that functions to adjust tonicity. NaCl in ANDA 212340 is an excipient that functions to adjust tonicity.

P.1 DESCRIPTION AND COMPOSITION

Composition table (updated on 6/11/2025)*

Unit Dose Composition of Iron Sucrose Injection, 50mg/2.5mL:

Ingredient	Function	Amount per mL	Amount per vial	% w/v	IIG[1] Limit (Injection)
Iron Sucrose	Active Pharmaceutical Ingredient	20 mg elemental iron	50 mg elemental iron	(b) (4)	
Sodium Hydroxide, NF	pH adjustment	q.s. to pH 10.5 – 11.1	q.s. to pH 10.5-11.1		
Water for Injection, USP			(b) (4)		

(b) (4)

Unit Dose Composition of Iron Sucrose Injection, 100mg/5mL:

Ingredient	Function	Amount per mL	Amount per vial	% w/v	IIG[1] Limit (Injection)
Iron Sucrose	Active Pharmaceutical Ingredient	20 mg elemental iron	100 mg elemental iron	(b) (4)	
Sodium Hydroxide, NF	pH Adjustment	q.s. to pH 10.5 – 11.1	q.s. to pH 10.5-11.1		
Water for Injection, USP			(b) (4)		

(b) (4)

Unit Dose Composition of Iron Sucrose Injection, 200mg/10mL:

Ingredient	Function	Amount per mL	Amount per vial	% w/v	IIG[1] Limit (Injection)
Iron Sucrose	Active Pharmaceutical Ingredient	20 mg elemental iron	200 mg elemental iron	(b) (4)	
Sodium Hydroxide, NF	pH Adjustment	q.s. to pH 10.5 – 11.1	q.s. to pH 10.5-11.1		
Water for Injection, USP			(b) (4)		

(b) (4)

(b) (4)

(b) (4)

Assessment (Review #3): **Adequate**

Assessment in Reviews ##1, 2

Note: RLD information not to be released via FOIA.

(b) (4)

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DRUG PRODUCT LIST OF DEFICIENCIES: NONE

Primary Drug Product Assessor Name and Date: Dahui Liu, Ph.D., 2/4/2020, 5/6/2020, 7/19/2021 (Review #2), 2/8/2022 (Review #2a), 12/12/2022 (Review #2b); Vasily Korotchenko, Ph.D., March 12, 2024 (Review #3), 07/10/2025 (Review #3a).

Secondary Assessor Name and Date (and Secondary Summary, as needed): Yiwei Li, Ph. D., OLDP/DLBPI/Branch II, (CR1) 02/12/2020, Shin Grace Chou 03/01/2022 (Review 2a), Cameron Smith (Review #2b), Dahui Liu, 3/12/2024 (Review #3), 07/10/2025 (Review #3a).

CHAPTER IV: LABELING

IQA ANDA Assessment Guide Reference

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

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

Is the drug product subject of a USP monograph? ☒ Yes ☐ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☒ Statement not needed

If NO, what is/are the needed statement(s)? _____

Update on 6/17/2025:

The firm updated section 11 as following. The description of the active ingredient and inactive ingredients is adequate.

"Each mL contains 20 mg elemental iron as iron sucrose in water for injection. Iron sucrose injection is available in 10 mL single-dose vials (200 mg elemental iron per 10 mL), 5 mL single-dose vials (100 mg elemental iron per 5 mL), and 2.5 mL single-dose vials (50 mg elemental iron per 2.5 mL). The drug product contains approximately 30% sucrose w/v (300 mg/mL) and sodium chloride for tonicity. Sodium hydroxide may be added to adjust pH to 10.5 to 11.1. The product contains no preservatives. The osmolarity of the injection is 1,250 mOsmol/L."

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

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

If "No," explain.

No update in Review #3.

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

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No ☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

No update in Review #3.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (MM)	Imprint Code

Send issue to the Labeling assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues:

Issue Description	Issue Reference Number or Link
N/A	N/A

LABELING LIST OF DEFICIENCIES: NONE

Primary Drug Product Assessor Name and Date: *Dahui Liu, Ph.D. 2/4/2020; Vasily Korotchenko, Ph.D., March 12, 2024 (Review #3), 07/10/2025 (Review #3a).*

Secondary Drug Product Assessor Name and Date: *Yiwei Li, Ph. D., OLDP/DLBPI/Branch II, (CR1) 02/12/2020; Dahui Liu, 3/12/2024 (Review #3), 07/10/2025 (Review #3a).*

Vasiliy Korotchenko

Digitally signed by Vasiliy Korotchenko
Date: 7/11/2025 10:43:38AM
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Dahui Liu

Digitally signed by Dahui Liu
Date: 7/18/2025 12:02:17PM
GUID: 54078879000a1ba887a7e24e53674214

MANUFACTURING INTEGRATED ASSESSMENT

Application ID	ANDA 212340
Drug Product Name	Iron Sucrose Injection, USP Eq. 20 mg base/mL
Strengths	50 mg/2.5 mL, 100 mg/5 mL, 200 mg/10 mL
Dosage Form	Injection
Administration Route	Intravenous
Indication	Iron sucrose injection is an iron replacement product indicated for the treatment of iron deficiency anemia in patients with chronic kidney disease (CKD).
Applicant Name	Sandoz Inc.
RLD Number	N021135

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate

Process Assessment Recommendation: Adequate

Assessment Summary:
DP manufacturer, (b) (4) , with NAI outcome and no 483 observation. (b) (4) Based on inspectional history and acceptable profile class, recommend approval. DS manufacturer, (b) (4) , PAI is completed and no 483 was issued, recommend approval.

Iron Sucrose Injection has three strengths (50 mg/2.5 mL, 100 mg/5 mL, and 200 mg/10 mL). Batch formula includes the API (iron sucrose), excipients (sodium hydroxide and water), (b) (4) .
Manufacturing process involves (b) (4)

(b) (4)

(b) (4)

[redacted]

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
Original (1)	8/28/2019
DRL Response BE 0006 (6)	04/16/2020
DP IR Response 0007 (7)	04/24/2020
CRL Response 0009 (9)	12/28/2020
IR Response 0010 (10)	12/7/2021
IR Response 0011 (11)	04/22/2022
IR Response 0012 (12)	07/06/2022
CRL Response 0013 (13)	08/18/2023

Highlight Key Issues from Last Cycle and Their Resolution:

- The visual inspection procedures were submitted and deemed adequate

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None

List Number of Comparability Protocols:
None

1. Lifecycle Management Considerations

Post-approval inspection?	No
Lifecycle considerations	No

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
(b) (4) [redacted]			Approve - Based on PAI
			Approve - Based on Previous History

(b) (4)	Approve - Based on Previous History
	Approve - Based on Previous History

II. (b) (4)

1. Batch Formula

2. **Batch Formula of Iron Sucrose Injection, USP 20mg/mL (50mg/2.5mL)**

Proposed Ingredient	(b) (4)	Amount per mL	% w/v	Theoretical Quantity for ANDA Batch	Theoretical Quantity for Proposed Commercial Batch
Iron Sucrose		Equivalent to 20 mg Elemental Iron Fe(III)	(b) (4)		(b) (4)
Sodium Hydroxide, NF		q.s. to pH 10.5-11.1			
Water for Injection, USP		(b) (4			(b) (4)

(b) (4)

3. **Batch formula of Iron Sucrose Injection, USP 20mg/mL (100mg/5mL)**

Proposed Ingredient	Amount per mL	% w/v	Theoretical Quantity for ANDA Batch	Theoretical Quantity for Proposed Commercial Batch
			Batch Size	
Iron Sucrose	Equivalent to 20 mg Elemental Iron Fe(III)			
Sodium Hydroxide, NF	q.s. to pH 10.5-11.1			
Water for Injection, USP				

4. **Batch formula of Iron Sucrose Injection, USP 20mg/mL (200mg/10mL)**

Proposed Ingredient	Amount per mL	% w/v	Theoretical Quantity for ANDA Batch	Theoretical Quantity for Proposed Commercial Batch
Iron Sucrose	Equivalent to 20 mg Elemental Iron Fe(III)			
Sodium Hydroxide, NF	q.s. to pH 10.5-11.1			
Water for Injection, USP				

Assessment: Adequate

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(b) (4)

V. List of Outstanding Information Request/Deficiencies:

Outstanding Deficiencies Collation Table
None.

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Wenchun Feng	Kamal Tiwari	2/10/2020	IR	TBD
2	Wenchun Feng	Kamal Tiwari	5/5/2020	CR Minor	Approve
3	Allison Aldridge	Rose Xu	7/9/2021	CR Minor	Approve
4	Allison Aldridge	Rose Xu	3/2/2022	Adequate	Approve
4	Allison Aldridge	Rose Xu	6/15/2022	IR	Approve
4	Allison Aldridge	Rose Xu	1/11/2023	Adequate	Approve
5	Allison Aldridge	Vidya Pai	7/29/2025	Adequate	Approve

Allison Aldridge

Digitally signed by Allison Aldridge
Date: 8/01/2025 08:43:14AM
GUID: 508da7170002981da764ca33dfb39a19

Vidya Pai

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VII: MICROBIOLOGY

IQA ANDA Assessment Guide Reference

Product Information	Sterile solution for multidose injection
ANDA Number	212340
Assessment Cycle Number	2
Drug Product Name / Strength	Iron Sucrose Injection, USP (50 mg/2.5 mL, 100 mg/5 mL, 200 mg/10 mL)
Route of Administration	Intravanous
Applicant Name	Sandoz Inc.
Manufacturing Site	(b) (4)
Method of Sterilization	

Assessment Recommendation: **Adequate**

Theme:

☒ N/A	☐ Depyrogenation Validation Data
☐ Product Sterility Assurance	☐ Product Release and/or Stability Specifications
☐ Media Fill Data	☐ Validation for Product Release and/or Stability Test Method
☐ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: *view justification statements found at:* **Justification Statements**

N/A
Other (Requires Division Director Approval) – *Assessor writes-in justification here if "other" selected as theme.*

Assessment Summary: The applicant has submitted a response to a Complete Response Letter dated June 29th, 2020. This review covers remaining issues from the previous cycle.

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received

eCTD 009	12/28/2020

Highlight Key Issues from Last Cycle and Their Resolution: (b) (4) [redacted].

Remarks: A Complete Response Letter (CRL) was issued to the applicant by the Agency on June 29th, 2020. Microbiology deficiencies were items # 17-30 in the CRL. The applicant's responses received December 24th, 2020 and are included and addressed in the appropriate sections of this review.

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): N/A

Supporting Documents: A212340MR01.pdf, dated February 10th, 2020 (Inadequate).

Select Number of Approved Comparability Protocols: 0

P.2.5 MICROBIOLOGICAL ATTRIBUTES

(b) (4)

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(b) (4)

Assessment: *Adequate*

MICROBIOLOGY LIST OF DEFICIENCIES

N/A

Primary Microbiology Assessor Name and Date:
Andrew Brown, Ph.D.
Microbiologist
CDER/OPQ/OPMA/DMAII/B5
March 13, 2023

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Denise Miller
Senior Product Quality Assessor
CDER/OPQ/OPMA/DMAII/B5
March 13, 2023

Andrew P Brown (OPQ)

Digitally signed by Andrew P Brown (OPQ)
Date: 8/11/2021 10:01:27AM
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Comments: Adequate

Bryan Riley

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Date: 8/11/2021 11:46:06AM
GUID: 503450f200004f5816a1d3ae902b5e91

Cameron Smith

Digitally signed by Cameron Smith
Date: 8/01/2025 12:02:02PM
GUID: 544e4d7a0002b355935ebaf76373f79e

Temitope Oriola

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ANDA Executive Summary

1. Application/Product Information

ANDA Number.	212340
Review Cycle #	3
Applicant Name	Sandoz Inc.
Drug Product Name	Iron Sucrose
Dosage Form. (click (+) for more than one)	Injection
Proposed Strength(s)	50 mg/2.5 mL, 100 mg/5 mL, 200 mg/10 mL
Route of Administration (click (+) for more than one)	Intravenous
Maximum Daily Dose	500 mg Fe, 8500 mg sucrose
Rx/OTC Dispensed	Rx
Proposed Indication	Iron sucrose injection is indicated for the treatment of iron deficiency anemia (IDA) in patients with chronic kidney disease (CKD).
Drug Product Description	Iron sucrose injection, USP, an iron replacement product, is a brown, sterile, aqueous, complex of polynuclear iron (III)-hydroxide in sucrose for intravenous use. Iron sucrose injection has a molecular weight of approximately 34,000 to 60,000 daltons and a proposed structural formula: $[Na_2Fe_5O_8(OH) \cdot 3(H_2O)]_n \cdot m(C_{12}H_{22}O_{11})$ where: n is the degree of iron polymerization and m is the number of sucrose molecules associated with the iron (III)-hydroxide. Each mL contains 20 mg elemental iron as iron sucrose in water for injection. Iron sucrose injection is available in 10 mL single-dose vials (200 mg elemental iron per 10 mL), 5 mL single-dose vials (100 mg elemental iron per 5 mL), and 2.5 mL single-dose vials (50 mg elemental iron per 2.5 mL). The drug product contains approximately 30% sucrose w/v (300 mg/mL) and has a pH of 10.5 to 11.1. The product contains no preservatives. The osmolarity of the injection is 1,250 mOsmol/L.

Co-packaged product information	N/A		
Device information, if any:	N/A		
Storage Temperature/ Conditions	Store in original carton at 20°C to 25°C (68° F to 77° F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not freeze.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Keduo Qian	Brian Connell
	Drug Product/ Labeling	Vasiliy Korotchenko	Dahui Liu
	Manufacturing	Allison Aldridge	Rose Xu
	Biopharmaceutics	N/A	N/A
	Microbiology	Andrew Brown	Denise Miller
	Other (specify):	N/A	N/A
	RBPM	Charmaine Flotildes	
	ATL	Dahui Liu	
Consults	**Discipline Consulted**	**Recommendation**	**Date**
	N/A		

2. Submission Document(s) Reviewed

Submission(s) Assessed	Document Date	Discipline(s) Affected
Resubmission/After Action- Complete; Quality/Quality Information; Quality/Microbiology Information	12/28/2020	All

Quality/Response To Information Request	12/07/2021	Drug Product, Manufacturing
Quality/Response To Information Request	04/22/2022	Drug Product, Manufacturing
Quality/Response To Information Request	07/06/2022	Drug Product, Manufacturing
Resubmission/After Action- Complete	08/18/2023	Drug Product
Response to Information Request	06/09/2025	Drug product, labeling
Response to Information Request	06/11/2025	Drug product, labeling
Response to Information Request	6/17/2025	Labeling
Previous Submission(s) Assessed	**Document Date**	**Discipline(s) Affected**
Original/Initial Submission (0001)	08/28/2019	All
Labeling/Response to Discipline Review Letter*	10/31/2019	Labeling
Bioequivalence/Response to Discipline Review Letter	04/16/2020	Drug Product
Quality/Response To Information Request	04/24/2020	Drug Product
Quality/Response to Discipline Review Letter	06/04/2020	Drug Product
* Scanned for quality information		

3. Related/Supporting Documents

a. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/ Comments
(b) (4)	II	(b) (4)	Iron Sucrose (b) (4) (b) (4)	Adequate	03/11/2024	R03 by Keduo Qian
	III			N/A		
	III			N/A		
	V			Adequate	01/06/2020	Review D018370M16 R01 by Valerie Huse
	III			N/A		

b. Other Documents: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description

NDA	N021135	RLD: Venofer® (Iron sucrose Injection, USP) by Luitpold Pharmaceuticals Inc. approved 20-MAR-2005.

4. Final Overall recommendation – Approval

Deficiencies (if applicable):

Overall Quality Deficiencies - Optional *(Deficiencies that affect multiple sub-disciplines; for subheadings use the format shown, for all deficiencies.)*

None

Drug Substance Deficiencies

None

Drug Product Deficiencies

None

Labeling Deficiencies *(Please contact OGD if you identify any Labeling deficiencies with your comments)*

None

Manufacturing Deficiencies

a. **Process:** None

b. **Facility:** None

Biopharmaceutics Deficiencies

N/A

Microbiology Deficiencies

None

Other Deficiencies *(Specify discipline, such as Environmental. For consults such as Biostatistics, PharmTox, CDRH, Clinical, etc., include consult type and specify Quality discipline – example:* ***Pharm/Tox consult for Drug Product****)*

None

Additional Comments:

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment(s) in your response: None

5. Basis for Recommendation

a. Summary of Rationale for Recommendation:

The application is approvable from CMC perspectives. The provided information for drug substance, drug product, manufacturing process, facility, and microbiology is adequate. The referenced DMF [redacted] (b) (4) is adequate. The stability data support the proposed 24 months shelf life. The provided comparative characterization data is adequate. The drug product is not impacted by NDSRIs.

b. Recommendation by Subdiscipline:

Drug Substance: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

Drug Product: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

Quality Labeling: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

Manufacturing: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

Biopharmaceutics: N/A

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

Microbiology: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

Environmental: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

6. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments: None

Comparability Protocols (PACMP): No
Comments: None

Additional Comments: [redacted] (b) (4) The PSG of this product has recommendations for comparative characterizations (both test product and RLD), which are conducted using three batches of test products manufactured using [redacted] (b) (4) Please refer to the PSG on recommendations on scale of batches used for comparative physicochemical characterizations, in vitro and in vivo BE studies.

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Dahui Liu

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MANUFACTURING INTEGRATED ASSESSMENT

Application ID	ANDA 212340
Drug Product Name	Iron Sucrose Injection, USP Eq. 20 mg base/mL
Strengths	50 mg/2.5 mL, 100 mg/5 mL, 200 mg/10 mL
Dosage Form	Injection
Administration Route	Intravenous
Indication	Iron sucrose injection is an iron replacement product indicated for the treatment of iron deficiency anemia in patients with chronic kidney disease (CKD).
Applicant Name	Sandoz Inc.
RLD Number	N021135

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate

Process Assessment Recommendation: Adequate

Assessment Summary:

DP manufacturer, [redacted] (b) (4) with NAI outcome and no 483 observation. [redacted] (b) (4) Based on inspectional history and acceptable profile class, recommend approval. DS manufacturer, [redacted] (b) (4) PAI is completed and no 483 was issued, recommend approval.

Iron Sucrose Injection has three strengths (50 mg/2.5 mL, 100 mg/5 mL, and 200 mg/10 mL). Batch formula includes the API (iron sucrose), excipients (sodium hydroxide and water), [redacted] (b) (4)

Manufacturing process involves [redacted] (b) (4)

[redacted] (b) (4)

(b) (4)

[redacted]

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
Original (1)	8/28/2019
DRL Response BE 0006 (6)	04/16/2020
DP IR Response 0007 (7)	04/24/2020
CRL Response 0009 (9)	12/28/2020
IR Response 0010 (10)	12/7/2021
IR Response 0011 (11)	04/22/2022
IR Response 0012 (12)	07/06/2022
CRL Response 0013 (13)	08/18/2023

Highlight Key Issues from Last Cycle and Their Resolution:

- The visual inspection procedures were submitted and deemed adequate

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None

List Number of Comparability Protocols:
None

1. Lifecycle Management Considerations

Post-approval inspection?	No
Lifecycle considerations	No

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
(b) (4) [redacted]			Approve - Based on PAI
			Approve - Based on Previous History

[redacted] (b) (4)	Approve - Based on Previous History
	Approve - Based on Previous History

II. [redacted] (b) (4)

1. Batch Formula

2. **Batch Formula of Iron Sucrose Injection, USP 20mg/mL (50mg/2.5mL)**

Proposed Ingredient	[redacted] (b) (4)	Amount per mL	% w/v	Theoretical Quantity for ANDA Batch	Theoretical Quantity for Proposed Commercial Batch
Iron Sucrose		Equivalent to 20 mg Elemental Iron Fe(III)	[redacted] (b) (4)	[redacted] (b) (4)	[redacted] (b) (4)
Sodium Hydroxide, NF		q.s. to pH 10.5-11.1	[redacted] (b) (4)	[redacted] (b) (4)	[redacted] (b) (4)
Water for Injection, USP			[redacted] (b) (4)	[redacted] (b) (4)	[redacted] (b) (4)

3. **Batch formula of Iron Sucrose Injection, USP 20mg/mL (100mg/5mL)**

Proposed Ingredient	Amount per mL	% w/v	Theoretical Quantity for ANDA Batch	Theoretical Quantity for Proposed Commercial Batch
			Batch Size	
Iron Sucrose	Equivalent to 20 mg Elemental Iron Fe(III)	(b) (4)	(b) (4)	
Sodium Hydroxide, NF	q.s. to pH 10.5-11.1			
Water for Injection, USP	(b) (4)			

(b) (4)

4. **Batch formula of Iron Sucrose Injection, USP 20mg/mL (200mg/10mL)**

Proposed Ingredient	Amount per mL	% w/v	Theoretical Quantity for ANDA Batch	Theoretical Quantity for Proposed Commercial Batch
Iron Sucrose	Equivalent to 20 mg Elemental Iron Fe(III)	(b) (4)	(b) (4)	
Sodium Hydroxide, NF	q.s. to pH 10.5-11.1			
Water for Injection, USP	(b) (4)			

(b) (4)

Assessment: Adequate

(b) (4)

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(b) (4)

V. List of Outstanding Information Request/Deficiencies:

Outstanding Deficiencies Collation Table
None.

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Wenchun Feng	Kamal Tiwari	2/10/2020	IR	TBD
2	Wenchun Feng	Kamal Tiwari	5/5/2020	CR Minor	Approve
3	Allison Aldridge	Rose Xu	7/9/2021	CR Minor	Approve
4	Allison Aldridge	Rose Xu	3/2/2022	Adequate	Approve
4	Allison Aldridge	Rose Xu	6/15/2022	IR	Approve
4	Allison Aldridge	Rose Xu	1/11/2023	Adequate	Approve
5	Allison Aldridge	Vidya Pai	7/29/2025	Adequate	Approve

Allison Aldridge

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Date: 8/01/2025 08:43:14AM
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Vidya Pai

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FDA U.S. FOOD & DRUG ADMINISTRATION

CHAPTER I: DRUG SUBSTANCE

IQA ANDA Assessment Guide Reference

Drug Substance Name	Iron (III) Hydroxide Sucrose Complex
ANDA Number	212340
Applicant Name	Sandoz Inc.
Assessment Cycle Number	3
DMF Number (If Applicable)	(b) (4)
DMF Status	Adequate
DMF Holder	(b) (4)

Assessment Recommendation: **Adequate**

Theme: N/A

Assessment Summary :

(b) (4). There is no monograph exists. The referenced DMF #33020 is assessed as Adequate per (b) (4)

See Assessment summary of the Drug Product section for citizen petition history and definition of active ingredient.

List Submissions being assessed (*Table*):

Document(s) Assessed	Date Received
Review #1	
Original submission, seq.#0001	8/28/2019
Amendment, seq. # 0002	10/31/2019
Review #2	
Amendment, Seq. #0009, response to CRL	12/28/2020
Amendment, Seq. #0010, response to IR	12/7/2021
Amendment, Seq. #0011, response to IR	4/22/2022
Amendment, Seq. #0012, response to process IR	7/6/2022
Review #3	

Multiple Categories / Subcategories, Sequence #13 (0013)	08-18-2023

Highlight Key Issues from Last Cycle and Their Resolution: DMF was inadequate in the previous cycle. Currently DMF is assessed as Adequate

Concise Description of Outstanding Issues: NONE

Select Number of Approved Comparability Protocols: 0

S.1 GENERAL INFORMATION

Generic Name	Iron Sucrose
Chemical Name(s)	Iron Sucrose – Iron Saccharate – Sucrose, Iron complex
Other Name(s)	Iron (III) – hydroxide sucrose complex
CAS Number	8047-67-4
Structure	Not Known Structure
Molecular Formula	$[Na_2Fe_5O_8\ (OH)\cdot 3(H_2O)]_n$. $m(C_{12}H_{22}O_{11})$
Molecular Weight	34000 – 60000 Da

Physical Appearance[1]	Homogenous brown-dark powder; Hygroscopic

(b) (4)

Assessment (Review #3): *Adequate*

(b) (4)

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No update in Chemistry Review #3.

R REGIONAL INFORMATION

Comparability Protocols: None

Assessment: N/A

Lifecycle Management Considerations

N/A

DRUG SUBSTANCE LIST OF DEFICIENCIES: NONE

Primary Drug Substance Assessor Name and Date: Dahui Liu, Ph.D. 1/30/2020 (Review 1), 7/19/2021 (Review #2), 2/3/2022 (Review #2a), 11/02/2022 (Review #2b); Vasily Korotchenko, Ph.D., March 12, 2024 (Review #3), 07/10/2025 (Review #3a).

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

Yiwei Li, Ph. D., OLDP/DLBPI/Branch II, (CR1) 02/12/2020, Shin Grace Chou 03/01/2022 (Review 2a), Cameron Smith (Review #2b), Dahui Liu, 3/12/2024 (Review #3), 07/10/2025 (Review #3a).

CHAPTER II: DRUG PRODUCT

IQA ANDA Assessment Guide Reference

Product Information	Iron Sucrose Injection, USP an iron replacement product, is a brown, sterile, aqueous solution, complex of polynuclear iron (III)-hydroxide in sucrose for intravenous use. Iron Sucrose Injection, USP has a molecular weight of approximately 34,000 to 60,000 Daltons and a proposed structural formula: $[Na_2Fe_5O_8(OH) \cdot 3(H_2O)]_n \cdot m(C_{12}H_{22}O_{11})$ where: n is the degree of iron polymerization and m is the number of sucrose molecules associated with the iron (III)-hydroxide. Each mL contains 20 mg elemental iron as iron sucrose in water for injection. Iron sucrose injection is available in 10 mL single-dose vials (200 mg elemental iron per 10 mL), 5 mL single-dose vials (100 mg elemental iron per 5 mL), and 2.5 mL single-dose vials (50 mg elemental iron per 2.5 mL). The drug product contains approximately 30% sucrose w/v (300 mg/mL) and has a pH of 10.5 to 11.1. The product contains no preservatives. The osmolarity of the injection is 1,250 mOsmol/L. The drug product is supplied sterile in 10 mL, 5 mL, and 2.5 mL single-dose vials. Each 10 mL vial contains 200 mg elemental iron, each 5 mL vial contains 100 mg elemental iron, and each 2.5 mL vial contains 50 mg elemental iron. Store in original carton at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). [see USP Controlled Room Temperature]. Do not freeze. There is USP monograph exists for the drug product.
ANDA Number	212340
Assessment Cycle Number	3a

Drug Product (DP) Name / Strength	Iron Sucrose Injection USP, 50 mg/2.5 mL, 100 mg/5 mL and 200 mg/10 mL
Route of Administration	Intravenous
Drug Product Manufacturer	Sandoz Inc..
RLD/RS Information (Brand Name of Product, Applicant)	Venofer/ LUITPOLD PHARMACEUTICALS INC
RLD/RS Number	NDA # 021135
Proposed Indication	Iron Sucrose Injection is indicated for the treatment of iron deficiency anemia in patients with chronic kidney disease (CKD)

Assessment Recommendation: **Adequate**

Theme: N/A

Assessment Summary:
The drug product is a USP item. The firm provided 24 months long term and 12 months intermediate stability data. All data meet the specification. No significant trend is observed at long term or intermediate conditions.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Review #1	
Original submission (Seq. # 0001)	08/28/2019
Amendment (Seq. # 0002), labeling	10/31/2019
Amendment (Seq. #0007), CCS sample shipment	4/24/2020
Review #2	
Amendment, (Seq. #0009), response to CRL	12/28/2020
Amendment, (Seq. #0010), response to IR	12/07/2021
Amendment, Seq. #0011, response to IR	4/22/2022
Amendment, Seq. #0012, response to IR	7/6/2022
Review #3 and 3a	
Multiple Categories / Subcategories, Sequence #13 (0013)	08-18-2023
Sequence #0017, response to IR	6/9/2025
Sequence #0018, response to IR	6/11/2025

Sequence #0019, response to IR	6/17/2025

Highlight Key Issues from Last Cycle and Their Resolution: Gross content specification is added, as requested.

Concise Description of Outstanding Issues (*List Bullet Points with Key Information and Update as Needed*): NONE

Select Number of Approved Comparability Protocols: 0

List Current Quality Endorsement Status:

- *USP monograph for Drug Product and compliance (current USP) – status: Adequate*
- *Dissolution status: N/A*
- *Elemental impurity compliance with ICH Q3D – status: Adequate*
- *Number of Comparability protocols included: 0*

Citizen Petition (CP) History

"Response Letter From FDA CDER to Foley Hoag LLP" was published on 5/26/2021 in response to citizen petition # FDA-2016-P-1163 regarding Velphoro, submitted on 4/19/2016. In the letter, the agency stated its conclusion that the active ingredient for Venofer is ferric oxyhydroxide.

On August 3, 2021, Vifor (International) Inc., Switzerland (Vifor) submitted a Citizen Petition and Petition for Stay (Vifor Petition) (FDA-2021-P-0893) requesting the Agency reverse certain actions announced in its Velphoro Citizen Petition response.

On July 1, 2024, the Agency published a memorandum stating that the Center for Drug Evaluation and Research (CDER) "is reevaluating its determination that the active ingredient of the iron products subject to the May 26, 2021, Citizen Petition response is ferric oxyhydroxide." The memorandum also stated that during the reevaluation period, "CDER is accepting the active ingredient names as approved prior to the May 26, 2021, Citizen Petition response for all iron products subject to the May 26, 2021, Citizen Petition response..." (See Docket Nos FDA-2016-P-1163 and FDA-2021-P-0893, available at regulations.gov.)

Active ingredient definition:

Based on further internal discussions and consideration of certain issues implicated by the above petitions,the Agency has now determined that the active ingredient in Venofer is iron sucrose, and that the active moiety is ferric oxyhydroxide.

Sodium Chloride (NaCl):

Upon further evaluation of the RLD Drug Substance components, it is OPQ's current understanding that NaCl is an excipient in the RLD that functions to adjust tonicity. NaCl in ANDA 212340 is an excipient that functions to adjust tonicity.

P.1 DESCRIPTION AND COMPOSITION

Composition table (updated on 6/11/2025)*

Unit Dose Composition of Iron Sucrose Injection, 50mg/2.5mL:

Ingredient	Function	Amount per mL	Amount per vial	% w/v	IIG[1] Limit (Injection)
Iron Sucrose	Active Pharmaceutical Ingredient	20 mg elemental iron	50 mg elemental iron	(b) (4)	
Sodium Hydroxide, NF	pH adjustment	q.s. to pH 10.5 – 11.1	q.s. to pH 10.5-11.1		
Water for Injection, USP	(b) (4)				

(b) (4)

Unit Dose Composition of Iron Sucrose Injection, 100mg/5mL:

Ingredient	Function	Amount per mL	Amount per vial	% w/v	IIG[1] Limit (Injection)
Iron Sucrose	Active Pharmaceutical Ingredient	20 mg elemental iron	100 mg elemental iron	(b) (4)	
Sodium Hydroxide, NF	pH Adjustment	q.s. to pH 10.5 – 11.1	q.s. to pH 10.5-11.1		
Water for Injection, USP	(b) (4)				

(b) (4)

Unit Dose Composition of Iron Sucrose Injection, 200mg/10mL:

Ingredient	Function	Amount per mL	Amount per vial	% w/v	IIG[1] Limit (Injection)
Iron Sucrose	Active Pharmaceutical Ingredient	20 mg elemental iron	200 mg elemental iron	(b) (4)	
Sodium Hydroxide, NF	pH Adjustment	q.s. to pH 10.5 – 11.1	q.s. to pH 10.5-11.1		
Water for Injection, USP	(b) (4)				

(b) (4)

(b) (4)

Assessment (Review #3): **Adequate**

Assessment in Reviews ##1, 2

Note: RLD information not to be released via FOIA.

(b) (4)

(b) (4)

This section is adequate.

****

Assessment in Review #3

(b) (4)

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(b) (4)

No update in Review #3.

REGIONAL INFORMATION

Environmental

Assessment: N/A

Methods Validation or Verification Package

Assessment: N/A

Comparability Protocols

Assessment: N/A

Lifecycle Management Considerations

(b) (4)

The PSG of this product has recommendations for comparative characterizations (both test product and RLD), which are conducted using three batches of test products manufactured using (b) (4)

DRUG PRODUCT LIST OF DEFICIENCIES: NONE

Primary Drug Product Assessor Name and Date: Dahui Liu, Ph.D., 2/4/2020, 5/6/2020, 7/19/2021 (Review #2), 2/8/2022 (Review #2a), 12/12/2022 (Review #2b); Vasily Korotchenko, Ph.D., March 12, 2024 (Review #3), 07/10/2025 (Review #3a).

Secondary Assessor Name and Date (and Secondary Summary, as needed): Yiwei Li, Ph. D., OLDP/DLBPI/Branch II, (CR1) 02/12/2020, Shin Grace Chou 03/01/2022 (Review 2a), Cameron Smith (Review #2b), Dahui Liu, 3/12/2024 (Review #3), 07/10/2025 (Review #3a).

CHAPTER IV: LABELING

IQA ANDA Assessment Guide Reference

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

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

Is the drug product subject of a USP monograph? ☒ Yes ☐ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☒ Statement not needed

If NO, what is/are the needed statement(s)? _____

Update on 6/17/2025:

The firm updated section 11 as following. The description of the active ingredient and inactive ingredients is adequate.

"Each mL contains 20 mg elemental iron as iron sucrose in water for injection. Iron sucrose injection is available in 10 mL single-dose vials (200 mg elemental iron per 10 mL), 5 mL single-dose vials (100 mg elemental iron per 5 mL), and 2.5 mL single-dose vials (50 mg elemental iron per 2.5 mL). The drug product contains approximately 30% sucrose w/v (300 mg/mL) and sodium chloride for tonicity. Sodium hydroxide may be added to adjust pH to 10.5 to 11.1. The product contains no preservatives. The osmolarity of the injection is 1,250 mOsmol/L."

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

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

If "No," explain.

No update in Review #3.

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

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No ☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

No update in Review #3.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (MM)	Imprint Code

Send issue to the Labeling assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues:

Issue Description	Issue Reference Number or Link
N/A	N/A

LABELING LIST OF DEFICIENCIES: NONE

Primary Drug Product Assessor Name and Date: *Dahui Liu, Ph.D. 2/4/2020; Vasily Korotchenko, Ph.D., March 12, 2024 (Review #3), 07/10/2025 (Review #3a).*

Secondary Drug Product Assessor Name and Date: *Yiwei Li, Ph. D., OLDP/DLBPI/Branch II, (CR1) 02/12/2020; Dahui Liu, 3/12/2024 (Review #3), 07/10/2025 (Review #3a).*

Vasiliy Korotchenko

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Date: 7/11/2025 10:43:38AM
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Dahui Liu

Digitally signed by Dahui Liu
Date: 7/18/2025 12:02:17PM
GUID: 54078879000a1ba887a7e24e53674214

ANDA Executive Summary

1. Application/Product Information

ANDA Number.	212340
Review Cycle #	3
Applicant Name	Sandoz Inc.
Drug Product Name	Iron Sucrose
Dosage Form. (click (+) for more than one)	Injection
Proposed Strength(s)	50 mg/2.5 mL, 100 mg/5 mL, 200 mg/10 mL
Route of Administration (click (+) for more than one)	Intravenous
Maximum Daily Dose	500 mg Fe, 8500 mg sucrose
Rx/OTC Dispensed	Rx
Proposed Indication	Iron sucrose injection is indicated for the treatment of iron deficiency anemia (IDA) in patients with chronic kidney disease (CKD).
Drug Product Description	Iron sucrose injection, USP, an iron replacement product, is a brown, sterile, aqueous, complex of polynuclear iron (III)-hydroxide in sucrose for intravenous use. Iron sucrose injection has a molecular weight of approximately 34,000 to 60,000 daltons and a proposed structural formula: $[Na_2Fe_5O_8(OH) \cdot 3(H_2O)]_n \cdot m(C_{12}H_{22}O_{11})$ where: n is the degree of iron polymerization and m is the number of sucrose molecules associated with the iron (III)-hydroxide. Each mL contains 20 mg elemental iron as iron sucrose in water for injection. Iron sucrose injection is available in 10 mL single-dose vials (200 mg elemental iron per 10 mL), 5 mL single-dose vials (100 mg elemental iron per 5 mL), and 2.5 mL single-dose vials (50 mg elemental iron per 2.5 mL). The drug product contains approximately 30% sucrose w/v (300 mg/mL) and has a pH of 10.5 to 11.1. The product contains no preservatives. The osmolarity of the injection is 1,250 mOsmol/L.

Co-packaged product information	N/A		
Device information, if any:	N/A		
Storage Temperature/ Conditions	Store in original carton at 20°C to 25°C (68° F to 77° F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not freeze.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Keduo Qian	Brian Connell
	Drug Product/ Labeling	Vasiliy Korotchenko	Dahui Liu
	Manufacturing	Allison Aldridge	Rose Xu
	Biopharmaceutics	N/A	N/A
	Microbiology	Andrew Brown	Denise Miller
	Other (specify):	N/A	N/A
	RBPM	Charmaine Flotildes	
	ATL	Dahui Liu	
Consults	**Discipline Consulted**	**Recommendation**	**Date**
	N/A		

2. Submission Document(s) Reviewed

Submission(s) Assessed	Document Date	Discipline(s) Affected
Resubmission/After Action- Complete; Quality/Quality Information; Quality/Microbiology Information	12/28/2020	All

Quality/Response To Information Request	12/07/2021	Drug Product, Manufacturing
Quality/Response To Information Request	04/22/2022	Drug Product, Manufacturing
Quality/Response To Information Request	07/06/2022	Drug Product, Manufacturing
Resubmission/After Action- Complete	08/18/2023	Drug Product
Previous Submission(s) Assessed	**Document Date**	**Discipline(s) Affected**
Original/Initial Submission (0001)	08/28/2019	All
Labeling/Response to Discipline Review Letter*	10/31/2019	Labeling
Bioequivalence/Response to Discipline Review Letter	04/16/2020	Drug Product
Quality/Response To Information Request	04/24/2020	Drug Product
Quality/Response to Discipline Review Letter	06/04/2020	Drug Product
* Scanned for quality information		

3. Related/Supporting Documents

a. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/ Comments
(b) (4)	II	(b) (4)	Iron Sucrose (b) (4)	Adequate	03/11/2024	R03 by Keduo Qian
	III		(b) (4)	N/A		
	III			N/A		
	V			Adequate	01/06/2020	Review D018370M16 R01 by Valerie Huse
	III			N/A		

b. Other Documents: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description
NDA	N021135	RLD: Venofer® (Iron sucrose Injection, USP) by Luitpold Pharmaceuticals Inc. approved 20-MAR-2005.

4. Final Overall recommendation – Approval

Deficiencies (if applicable):

Overall Quality Deficiencies - Optional *(Deficiencies that affect multiple sub-disciplines; for subheadings use the format shown, for all deficiencies.)*

None

Drug Substance Deficiencies

None

Drug Product Deficiencies

None

Labeling Deficiencies *(Please contact OGD if you identify any Labeling deficiencies with your comments)*

None

Manufacturing Deficiencies

a. **Process:** None

b. **Facility:** None

Biopharmaceutics Deficiencies

N/A

Microbiology Deficiencies

None

Other Deficiencies *(Specify discipline, such as Environmental. For consults such as Biostatistics, PharmTox, CDRH, Clinical, etc., include consult type and specify Quality discipline – example:* ***Pharm/Tox consult for Drug Product****)*

None

Additional Comments:

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment(s) in your response: None

5. Basis for Recommendation

a. Summary of Rationale for Recommendation:

The application is approvable from CMC perspectives. The provided information for drug substance, drug product, manufacturing process, facility, and microbiology is adequate. The referenced DMF [redacted] (b) (4) is adequate. The stability data support the proposed 24 months shelf life. The provided comparative characterization data is adequate. The drug product is not impacted by NDSRIs.

b. Recommendation by Subdiscipline:

Drug Substance: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

Drug Product: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

Quality Labeling: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

Manufacturing: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

Biopharmaceutics: N/A

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

Microbiology: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

Environmental: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

6. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments: None

Comparability Protocols (PACMP): No
Comments: None

Additional Comments: [redacted] (b) (4) The PSG of this product has recommendations for comparative characterizations (both test product and RLD), which are conducted using three batches of test products manufactured using [redacted] (b) (4) Please refer to the PSG on recommendations on scale of batches used for comparative physicochemical characterizations, in vitro and in vivo BE studies.

[redacted] (b) (4)

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FDA U.S. FOOD & DRUG ADMINISTRATION

CHAPTER I: DRUG SUBSTANCE

IQA ANDA Assessment Guide Reference

Drug Substance Name	Iron (III) Hydroxide Sucrose Complex
ANDA Number	212340
Applicant Name	Sandoz Inc.
Assessment Cycle Number	3
DMF Number (If Applicable)	(b) (4)
DMF Status	Adequate
DMF Holder	(b) (4)

Assessment Recommendation: **Adequate**

Theme: N/A

Assessment Summary :

(b) (4). There is no monograph exists. The referenced DMF #33020 is assessed as Adequate per (b) (4).

"Response Letter From FDA CDER to Foley Hoag LLP" is published on 5/26/2021 in response to citizen petition # FDA-2016-P-1163 regarding Velphoro. In the letter, the agency reiterate the API for Venofer is ferric oxyhydroxide. A comment was sent to the applicant regarding the definition of API for iron sucrose product in the IR letter dated 10/26/2021 and the firm acknowledged it.

List Submissions being assessed (*Table*):

Document(s) Assessed	Date Received
Review #1	
Original submission, seq.#0001	8/28/2019
Amendment, seq. # 0002	10/31/2019
Review #2	
Amendment, Seq. #0009, response to CRL	12/28/2020
Amendment, Seq. #0010, response to IR	12/7/2021
Amendment, Seq. #0011, response to IR	4/22/2022

Amendment, Seq. #0012, response to process IR	7/6/2022
Review #3	
Multiple Categories / Subcategories, Sequence #13 (0013)	08-18-2023

Highlight Key Issues from Last Cycle and Their Resolution: DMF was inadequate in the previous cycle. Currently DMF is assessed as Adequate

Concise Description of Outstanding Issues: NONE

Select Number of Approved Comparability Protocols: 0

S.1 GENERAL INFORMATION

Generic Name	Iron Sucrose
Chemical Name(s)	Iron Sucrose – Iron Saccharate – Sucrose, Iron complex
Other Name(s)	Iron (III) – hydroxide sucrose complex
CAS Number	8047-67-4
Structure	Not Known Structure
Molecular Formula	$[Na_2Fe_5O_8\ (OH)\bullet 3(H_20)]_n$. $m(C_{12}H_{22}O_{11})$
Molecular Weight	34000 – 60000 Da

Physical Appearance[1]	Homogenous brown-dark powder; Hygroscopic
	(b) (4)

Assessment (Review #3): *Adequate*

Assessment in Reviews 1, 2

(b) (4)

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No update in Chemistry Review #3.

R REGIONAL INFORMATION

Comparability Protocols: None

Assessment: N/A

Lifecycle Management Considerations

N/A

DRUG SUBSTANCE LIST OF DEFICIENCIES: NONE

Primary Drug Substance Assessor Name and Date: Dahui Liu, Ph.D. 1/30/2020 (Review 1), 7/19/2021 (Review #2), 2/3/2022 (Review #2a), 11/02/2022 (Review #2b); Vasily Korotchenko, Ph.D., March 12, 2024 (Review #3)

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

Yiwei Li, Ph. D., OLDP/DLBPI/Branch II, (CR1) 02/12/2020, Shin Grace Chou 03/01/2022 (Review 2a), Cameron Smith (Review #2b), Dahui Liu, 3/12/2024 (Review #3)

CHAPTER II: DRUG PRODUCT

IQA ANDA Assessment Guide Reference

Product Information	Iron Sucrose Injection, USP an iron replacement product, is a brown, sterile, aqueous solution, complex of polynuclear iron (III)-hydroxide in sucrose for intravenous use. Iron Sucrose Injection, USP has a molecular weight of approximately 34,000 to 60,000 Daltons and a proposed structural formula: $[Na_2Fe_5O_8(OH) \cdot 3(H_2O)]_n \cdot m(C_{12}H_{22}O_{11})$ where: n is the degree of iron polymerization and m is the number of sucrose molecules associated with the iron (III)-hydroxide. Each mL contains 20 mg elemental iron as iron sucrose in water for injection. Iron sucrose injection is available in 10 mL single-dose vials (200 mg elemental iron per 10 mL), 5 mL single-dose vials (100 mg elemental iron per 5 mL), and 2.5 mL single-dose vials (50 mg elemental iron per 2.5 mL). The drug product contains approximately 30% sucrose w/v (300 mg/mL) and has a pH of 10.5 to 11.1. The product contains no preservatives. The osmolarity of the injection is 1,250 mOsmol/L. The drug product is supplied sterile in 10 mL, 5 mL, and 2.5 mL single-dose vials. Each 10 mL vial contains 200 mg elemental iron, each 5 mL vial contains 100 mg elemental iron, and each 2.5 mL vial contains 50 mg elemental iron. Store in original carton at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). [see USP Controlled Room Temperature]. Do not freeze. There is USP monograph exists for the drug product.
ANDA Number	212340
Assessment Cycle Number	3

Drug Product (DP) Name / Strength	Iron Sucrose Injection USP, 50 mg/2.5 mL, 100 mg/5 mL and 200 mg/10 mL
Route of Administration	Intravenous
Drug Product Manufacturer	Sandoz Inc..
RLD/RS Information (Brand Name of Product, Applicant)	Venofer/ LUITPOLD PHARMACEUTICALS INC
RLD/RS Number	NDA # 021135
Proposed Indication	Iron Sucrose Injection is indicated for the treatment of iron deficiency anemia in patients with chronic kidney disease (CKD)

Assessment Recommendation: **Adequate**

Theme: N/A

Assessment Summary:
The drug product is a USP item. The firm provided 24 months long term and 12 months intermediate stability data. All data meet the specification. No significant trend is observed at long term or intermediate ocnditions.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Review #1	
Original submission (Seq. # 0001)	08/28/2019
Amendment (Seq. # 0002), labeling	10/31/2019
Amendment (Seq. #0007), CCS sample shipment	4/24/2020
Review #2	
Amendment, (Seq. #0009), response to CRL	12/28/2020
Amendment, (Seq. #0010), response to IR	12/07/2021
Amendment, Seq. #0011, response to IR	4/22/2022
Amendment, Seq. #0012, response to IR	7/6/2022
Review #3	
Multiple Categories / Subcategories, Sequence #13 (0013)	08-18-2023

Highlight Key Issues from Last Cycle and Their Resolution: Gross content specification is added, as requested.

Concise Description of Outstanding Issues (*List Bullet Points with Key Information and Update as Needed*): NONE

Select Number of Approved Comparability Protocols: 0

List Current Quality Endorsement Status:

- *USP monograph for Drug Product and compliance (current USP) – status: Adequate*
- *Dissolution status: N/A*
- *Elemental impurity compliance with ICH Q3D – status: Adequate*
- *Number of Comparability protocols included: 0*

P.1 DESCRIPTION AND COMPOSITION

Iron Sucrose Injection, USP Eq. to 20 mg base/mL	
Strength	**Product Description**
Ferric Oxyhydroxide Injection, USP Eq. to 20 mg base/mL	50 mg elemental iron per 2.5 mL, in a 5 mL single-use vial
	100 mg elemental iron per 5 mL, in a 5 mL single-use vial
	200 mg elemental iron per 10 mL, in a 10 mL single-use vial

Unit Dose Composition of Ferric Oxyhydroxide Injection (Updated in nSequence 0013)

Ingredient	Function	Amount per mL	Amount per vial			% w/v	IIG[1] Limit (Injection)
			50 mg/2.5 mL vial	100 mg/5.0 mL vial	200 mg/10.0 mL vial		
Ferric Oxyhydroxide	Active Pharmaceutical Ingredient	20 mg elemental iron	50 mg elemental iron	100 mg elemental iron	200 mg elemental iron	(b) (4)	
(b) (4)							
Sodium Hydroxide, NF	pH adjustment	q.s. to pH 10.5 – 11.1	q.s. to pH 10.5-11.1				
Water for Injection, USP	(b) (4)						
(b) (4)							

Assessment (Review #3): Adequate

Assessment in Reviews ##1, 2

Note: RLD information not to be released via FOIA.

(b) (4)

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No update in Review #3.

REGIONAL INFORMATION

Environmental

Assessment: N/A

Methods Validation or Verification Package

Assessment: N/A

Comparability Protocols

Assessment: N/A

Lifecycle Management Considerations

N/A

DRUG PRODUCT LIST OF DEFICIENCIES: NONE

Primary Drug Product Assessor Name and Date: Dahui Liu, Ph.D., 2/4/2020, 5/6/2020, 7/19/2021 (Review #2), 2/8/2022 (Review #2a), 12/12/2022 (Review #2b); Vasily Korotchenko, Ph.D., March 12, 2024 (Review #3)

Secondary Assessor Name and Date (and Secondary Summary, as needed): Yiwei Li, Ph. D., OLDP/DLBPI/Branch II, (CR1) 02/12/2020, Shin Grace Chou 03/01/2022 (Review 2a), Cameron Smith (Review #2b), Dahui Liu, 3/12/2024 (Review #3)

CHAPTER IV: LABELING

IQA ANDA Assessment Guide Reference

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

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

Is the drug product subject of a USP monograph? ☒ Yes ☐ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☒ Statement not needed

If NO, what is/are the needed statement(s)? _____

No update in Review #3.

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

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

If "No," explain.

No update in Review #3.

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

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

No update in Review #3.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (MM)	Imprint Code

Send issue to the Labeling assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues:

Issue Description	Issue Reference Number or Link
N/A	N/A

LABELING LIST OF DEFICIENCIES: NONE

Primary Drug Product Assessor Name and Date: Dahui Liu, Ph.D. 2/4/2020

Secondary Drug Product Assessor Name and Date:

Yiwei Li, Ph. D., OLDP/DLBPI/Branch II, (CR1) 02/12/2020

Dahui Liu

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Vasiliy Korotchenko

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Date: 3/13/2024 04:36:48PM
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ANDA Executive Summary

1. Application/Product Information

ANDA Number.	212340
Review Cycle #	2
Applicant Name	Sandoz Inc.
Drug Product Name	Iron Sucrose
Dosage Form. (click (+) for more than one)	Injection
Proposed Strength(s)	50 mg/2.5 mL, 100 mg/5 mL, 200 mg/10 mL
Route of Administration (click (+) for more than one)	Intravenous
Maximum Daily Dose	500 mg Fe, 8500 mg sucrose
Rx/OTC Dispensed	Rx
Proposed Indication	Iron sucrose injection is indicated for the treatment of iron deficiency anemia (IDA) in patients with chronic kidney disease (CKD).
Drug Product Description	Iron sucrose injection, USP, an iron replacement product, is a brown, sterile, aqueous, complex of polynuclear iron (III)-hydroxide in sucrose for intravenous use. Iron sucrose injection has a molecular weight of approximately 34,000 to 60,000 daltons and a proposed structural formula: $[Na_2Fe_5O_8(OH) \cdot 3(H_2O)]_n \cdot m(C_{12}H_{22}O_{11})$ where: n is the degree of iron polymerization and m is the number of sucrose molecules associated with the iron (III)-hydroxide. Each mL contains 20 mg elemental iron as iron sucrose in water for injection. Iron sucrose injection is available in 10 mL single-dose vials (200 mg elemental iron per 10 mL), 5 mL single-dose vials (100 mg elemental iron per 5 mL), and 2.5 mL single-dose vials (50 mg elemental iron per 2.5 mL). The drug product contains approximately 30% sucrose w/v (300 mg/mL) and has a pH of 10.5 to 11.1. The product contains no preservatives. The osmolarity of the injection is 1,250 mOsmol/L.

Co-packaged product information	N/A		
Device information, if any:	N/A		
Storage Temperature/ Conditions	Store in original carton at 20°C to 25°C (68° F to 77° F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not freeze.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Keduo Qian	Deborah Johnson
	Drug Product/ Labeling	Dahui Liu	Cameron Smith
	Manufacturing	Allison Aldridge	Rose Xu
	Biopharmaceutics	N/A	N/A
	Microbiology	Andrew Brown	Denise Miller
	Other (specify):	N/A	N/A
	RBPM	Erin Andrews	
	ATL	Cameron Smith	
Consults	**Discipline Consulted**	**Recommendation**	**Date**
	N/A		

2. Submission Document(s) Reviewed

Submission(s) Assessed	Document Date	Discipline(s) Affected
Resubmission/After Action- Complete; Quality/Quality Information; Quality/Microbiology Information (0009)	12/28/2020	All

Quality/Response To Information Request (0010)	12/07/2021	Drug Product, Manufacturing
Quality/Response To Information Request (0011)	04/22/2022	Drug Product, Manufacturing
Quality/Response To Information Request (0012)	07/06/2022	Drug Product, Manufacturing
Previous Submission(s) Assessed	**Document Date**	**Discipline(s) Affected**
Original/Initial Submission (0001)	08/28/2019	All
Labeling/Response to Discipline Review Letter* (0002)	10/31/2019	Labeling
Bioequivalence/Response to Discipline Review Letter (0006)	04/16/2020	Drug Product
Quality/Response To Information Request (0007)	04/24/2020	Drug Product
Quality/Response to Discipline Review Letter (0008)	06/04/2020	Drug Product
* Scanned for quality information		

3. Related/Supporting Documents

a. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/ Comments
(b) (4)	II	(b) (4)	Iron Sucrose ((b) (4)	Inadequate -Major	08/12/2021	Review #2 by Keduo Qian
	III		(b) (4)	N/A		
	III			N/A		
	V			Adequate	01/06/2020	Review D018370M16 R01 by Valerie Huse
	III			N/A		

b. Other Documents: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description
NDA	N021135	RLD: Venofer® (Iron sucrose Injection, USP) by Luitpold Pharmaceuticals Inc. approved 20-MAR-2005.

4. Final Overall recommendation – Complete Response-Major

Deficiencies (if applicable):

Overall Quality Deficiencies

None.

Drug Substance Deficiencies

1. [redacted] (b) (4)

[redacted] (b) (4)

Drug Product Deficiencies

1. [redacted] (b) (4)

Labeling Deficiencies

None.

Manufacturing Deficiencies

None.

Biopharmaceutics Deficiencies

N/A

Microbiology Deficiencies

None.

Other Deficiencies

None.

Additional Comments:

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment(s) in your response:

None.

5. Basis for Recommendation

a. Summary of Rationale for Recommendation:

The application is not recommended for approval due to quality related deficiencies summarized in Section 4. OPQ recommends issuing a Complete Response Letter – Major.

b. Recommendation by Subdiscipline:

Drug Substance: INADEQUATE-MAJOR

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

(b) (4)

Drug Product: INADEQUATE-MINOR

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

Quality Labeling: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

Manufacturing: ADEQUATE

Process: Adequate

Facilities: Adequate

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

Biopharmaceutics: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

Microbiology: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

Environmental: N/A

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

6. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments: N/A

Comparability Protocols (PACMP): No
Comments: N/A

Additional Comments: N/A

Cameron Smith

Digitally signed by Cameron Smith
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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER I: DRUG SUBSTANCE

IQA ANDA Assessment Guide Reference

Drug Substance Name	Iron (III) Hydroxide Sucrose Complex
ANDA Number	212340
Applicant Name	Sandoz Inc.
Assessment Cycle Number	2b
DMF Number (If Applicable)	33020
DMF Status (review of amendment dated 11/26/2021 is deferred to the next cycle.)	Inadequate - Major
DMF Holder	Opocrin S.p.A.

Assessment Recommendation: **Inadequate - Major**

Theme:

☐ N/A	☐ Other (Requires Division Director Approval)
☒ DMF	☐ Due to Consult
☐ New DS Batch	

Justification: *view justification statements found at:* **Justification Statements**

The Pharmaceutical Quality deficiencies have been classified as MAJOR due to the nature of the deficiencies identified in Drug Master File (DMF) (b) (4) (see guidance for industry, ANDA Submissions – Amendments to Abbreviated New Drug Applications Under GDUFA). The deficiencies were communicated to the DMF holder in a separate Complete Response Letter. Contact the referenced DMF holder for more information

Assessment Summary:

(b) (4).

There is no monograph exists. The referenced DMF (b) (4) is last reviewed by Qian, Keduo on 8/12/2021 and found inadequate major. The review of the DMF quality amendment dated 11/26/2021 is deferred to the next review cycle.The drug substance section is inadequate due to inadequate DMF.

"Response Letter From FDA CDER to Foley Hoag LLP" is published on 5/26/2021 in response to citizen petition # FDA-2016-P-1163 regarding Velphoro. In the letter, the agency reiterate the API for Venofer is ferric oxyhydroxide. A comment was sent to the applicant regarding the definition of API for iron sucrose product in the IR letter dated 10/26/2021 and the firm acknowledged it.

List Submissions being assessed (*Table*):

Document(s) Assessed	Date Received
Review #1	
Original submission, seq.#0001	8/28/2019
Amendment, seq. # 0002	10/31/2019
Review #2	
Amendment, Seq. #0009, response to CRL	12/28/20
Amendment, Seq. #0010, response to IR	12/7/2021
Amendment, Seq. #0011, response to IR	4/6/2022
Amendment, Seq. #0012, response to process IR	7/6/2022

Highlight Key Issues from Last Cycle and Their Resolution: The section is inadequate due to inadequate DMF (major) and minor deficiencies in specification.

Concise Description of Outstanding Issues:

- DMF is inadequate major.

Select Number of Approved Comparability Protocols: 0

S.1 GENERAL INFORMATION

Generic Name	Iron Sucrose
Chemical Name(s)	Iron Sucrose – Iron Saccharate – Sucrose, Iron complex
Other Name(s)	Iron (III) – hydroxide sucrose complex
CAS Number	8047-67-4
Structure	Not Known Structure
Molecular Formula	$[Na_2Fe_5O_8 (OH)\cdot 3(H_20)]_n . m(C_{12}H_{22}O_{11})$
Molecular Weight	34000 – 60000 Da

Physical Appearance[1]	Homogenous brown-dark powder; Hygroscopic

(b) (4)

[redacted]

Assessment (Review #1): *Adequate*

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(b) (4)

[redacted]

R REGIONAL INFORMATION

Comparability Protocols: None

Assessment: N/A

Lifecycle Management Considerations

N/A

DRUG SUBSTANCE LIST OF DEFICIENCIES

1. (b) (4)

[redacted]

.

(b) (4)

[redacted]

(b) (4)

Primary Drug Substance Assessor Name and Date: Dahui Liu, Ph.D. 1/30/2020 (Review 1), 7/19/2021 (Review #2), 2/3/2022 (Review #2a), 11/02/2022 (Review #2b)

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

Yiwei Li, Ph. D., OLDP/DLBPI/Branch II, (CR1) 02/12/2020, Shin Grace Chou 03/01/2022 (Review 2a), Cameron Smith (Review #2b)

CHAPTER II: DRUG PRODUCT

IQA ANDA Assessment Guide Reference

Product Information	Iron Sucrose Injection, USP an iron replacement product, is a brown, sterile, aqueous solution, complex of polynuclear iron (III)-hydroxide in sucrose for intravenous use. Iron Sucrose Injection, USP has a molecular weight of approximately 34,000 to 60,000 Daltons and a proposed structural formula: $[Na_2Fe_5O_8(OH) \cdot 3(H_2O)]_n \cdot m(C_{12}H_{22}O_{11})$ where: n is the degree of iron polymerization and m is the number of sucrose molecules associated with the iron (III)-hydroxide. Each mL contains 20 mg elemental iron as iron sucrose in water for injection. Iron sucrose injection is available in 10 mL single-dose vials (200 mg elemental iron per 10 mL), 5 mL single-dose vials (100 mg elemental iron per 5 mL), and 2.5 mL single-dose vials (50 mg elemental iron per 2.5 mL). The drug product contains approximately 30% sucrose w/v (300 mg/mL) and has a pH of 10.5 to 11.1. The product contains no preservatives. The osmolarity of the injection is 1,250 mOsmol/L. The drug product is supplied sterile in 10 mL, 5 mL, and 2.5 mL single-dose vials. Each 10 mL vial contains 200 mg elemental iron, each 5 mL vial contains 100 mg elemental iron, and each 2.5 mL vial contains 50 mg elemental iron. Store in original carton at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). [see USP Controlled Room Temperature]. Do not freeze. There is USP monograph exists for the drug product.
ANDA Number	212340

Assessment Cycle Number	2b
Drug Product (DP) Name / Strength	Iron Sucrose Injection USP, 50 mg/2.5 mL, 100 mg/5 mL and 200 mg/10 mL
Route of Administration	Intravenous
Drug Product Manufacturer	Sandoz Inc..
RLD/RS Information (Brand Name of Product, Applicant)	Venofer/ LUITPOLD PHARMACEUTICALS INC
RLD/RS Number	NDA # 021135
Proposed Indication	Iron Sucrose Injection is indicated for the treatment of iron deficiency anemia in patients with chronic kidney disease (CKD)

Assessment Recommendation: **Inadequate - Minor**

Theme:

☒ N/A	☐ Unacceptable Analytical Methods
☐ Unqualified Impurity	☐ Application Quality
☐ New DP Batch	☐ Pharmaceutical Equivalence
☐ Product Design	☐ Product Safety
☐ Failing Stability Data	☐ Other (Requires Division Director Approval)
☐ Application Completeness	☐ Due to Consult

Justification: *view justification statements found at:* **Justification Statements**

N/A

Assessment Summary:
The drug product is a USP item. The firm provided 24 months long term and 12 months intermediate stability data. All data meet the specification. No significant trend is observed at long term or intermediate ocnditions. The drug product section is inadequate with one minor deficieny in specification.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Review #1	
Original submission (Seq. # 0001)	**08/28/2019**
Amendment (Seq. # 0002), labeling	**10/31/2019**
Amendment (Seq. #0007), CCS sample shipment	**4/24/2020**
Review #2	

Amendment, (Seq. #0009), response to CRL	**12/28/2020**
Amendment, (Seq. #0010), response to IR	**12/07/2021**
Amendment, Seq. #0011, response to IR	4/6/2022
Amendment, Seq. #0012, response to IR	7/6/2022

Highlight Key Issues from Last Cycle and Their Resolution: The drug product section is inadequate with minor deficiencies in the comparative physicochemical characterization study, specification, and analytical method.

Concise Description of Outstanding Issues (*List Bullet Points with Key Information and Update as Needed*): The drug product section is inadequate due to one minor deficiency in specification.

Select Number of Approved Comparability Protocols: 0

List Current Quality Endorsement Status:

- *USP monograph for Drug Product and compliance (current USP) – status: Adequate*
- *Dissolution status: N/A*
- *Elemental impurity compliance with ICH Q3D – status: Adequate*
- *Number of Comparability protocols included: 0*

P.1 DESCRIPTION AND COMPOSITION

Ingredient	Function	Amount per mL	Amount per vial			% w/v	IIG[1] Limit (Injection)
			50 mg/2.5 mL vial	100 mg/5.0 mL vial	200 mg/10.0 mL vial		
Iron Sucrose	Active Pharmaceutical Ingredient	20 mg elemental iron	50 mg elemental iron	100 mg elemental iron	200 mg elemental iron	(b) (4)	
Sodium Hydroxide, NF	pH adjustment	q.s. to pH 10.5 – 11.1	q.s. to pH 10.5-11.1				
Water for Injection, USP							

(b) (4)

Assessment: Adequate
Note: RLD information not to be released via FOIA.

(b) (4)

This section is adequate.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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REGIONAL INFORMATION

Environmental

Assessment: N/A

Methods Validation or Verification Package

Assessment: N/A

Comparability Protocols

Assessment: N/A

Lifecycle Management Considerations

N/A

DRUG PRODUCT LIST OF DEFICIENCIES

(b) (4)

Primary Drug Product Assessor Name and Date: Dahui Liu, Ph.D., 2/4/2020, 5/6/2020, 7/19/2021 (Review #2), 2/8/2022 (Review #2a), 12/12/2022 (Review #2b)

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

Yiwei Li, Ph. D., OLDP/DLBPI/Branch II, (CR1) 02/12/2020, Shin Grace Chou 03/01/2022 (Review 2a), Cameron Smith (Review #2b)

CHAPTER IV: LABELING

IQA ANDA Assessment Guide Reference

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

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

Is the drug product subject of a USP monograph? ☒ Yes ☐ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☒ Statement not needed

If NO, what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

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:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (MM)	Imprint Code

Send issue to the Labeling assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues:

Issue Description	Issue Reference Number or Link
N/A	N/A

LABELING LIST OF DEFICIENCIES

None

Primary Drug Product Assessor Name and Date: Dahui Liu, Ph.D. 2/4/2020

Secondary Drug Product Assessor Name and Date:

Yiwei Li, Ph. D., OLDP/DLBPI/Branch II, (CR1) 02/12/2020

Dahui Liu

Digitally signed by Dahui Liu
Date: 3/09/2023 04:31:09PM
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Cameron Smith

Digitally signed by Cameron Smith
Date: 3/09/2023 04:36:03PM
GUID: 544e4d7a0002b355935ebaf76373f79e

MANUFACTURING INTEGRATED ASSESSMENT

Application ID	ANDA 212340
Drug Product Name	Iron Sucrose Injection, USP Eq. 20 mg base/mL
Strengths	50 mg/2.5 mL, 100 mg/5 mL, 200 mg/10 mL
Dosage Form	Injection
Administration Route	Intravenous
Indication	Iron sucrose injection is an iron replacement product indicated for the treatment of iron deficiency anemia in patients with chronic kidney disease (CKD).
Applicant Name	Sandoz Inc.
RLD Number	N021135

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate

Process Assessment Recommendation: Adequate

Assessment Summary:
DP manufacturer, [redacted] (b) (4) most recent inspection [redacted] (b) (4) is PAI for SVS profile class, with NAI outcome and no 483 observation. [redacted] (b) (4) Based on inspectional history and acceptable profile class, recommend approval. DS manufacturer, [redacted] (b) (4), PAI is completed and no 483 was issued, recommend approval.

Iron Sucrose Injection has three strengths (50 mg/2.5 mL, 100 mg/5 mL, and 200 mg/10 mL). Batch formula includes the API (iron sucrose), excipients (sodium hydroxide and water), [redacted] (b) (4) .
Manufacturing process involves [redacted] (b) (4)

[redacted] (b) (4)

(b) (4)

[redacted]

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
Original (1)	8/28/2019
DRL Response BE 0006 (6)	04/16/2020
DP IR Response 0007 (7)	04/24/2020
CRL Response 0009 (9)	12/28/2020
IR Response 0010 (10)	12/7/2021
IR Response 0011 (11)	04/22/2022
IR Response 0012 (12)	07/06/2022

Highlight Key Issues from Last Cycle and Their Resolution:

- The visual inspection procedures were submitted and deemed adequate

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None

List Number of Comparability Protocols:
None

1. Lifecycle Management Considerations

Post-approval inspection?	No
Lifecycle considerations	No

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
(b) (4) [redacted]			Approve - Based on PAI
[redacted]			Approve - Based on Previous History
[redacted]			Approve - Based on

(b) (4)	Previous History
	Approve - Based on Previous History

II. (b) (4)

1. Batch Formula

2. **Batch Formula of Iron Sucrose Injection, USP 20mg/mL (50mg/2.5mL)**

Proposed Ingredient	(b) (4)	Amount per mL	% w/v	Theoretical Quantity for ANDA Batch	Theoretical Quantity for Proposed Commercial Batch
Iron Sucrose		Equivalent to 20 mg Elemental Iron Fe(III)			(b) (4)
Sodium Hydroxide, NF		q.s. to pH 10.5-11.1			
Water for Injection, USP				(b) (4)	
					(b) (4)
				(b) (4)	

3. **Batch formula of Iron Sucrose Injection, USP 20mg/mL (100mg/5mL)**

Proposed Ingredient	Amount per mL	% w/v	Theoretical Quantity for ANDA Batch	Theoretical Quantity for Proposed Commercial Batch
			Batch Size	
Iron Sucrose	Equivalent to 20 mg Elemental Iron Fe(III)			
Sodium Hydroxide, NF	q.s. to pH 10.5-11.1			
Water for Injection, USP				

4. **Batch formula of Iron Sucrose Injection, USP 20mg/mL (200mg/10mL)**

Proposed Ingredient	Amount per mL	% w/v	Theoretical Quantity for ANDA Batch	Theoretical Quantity for Proposed Commercial Batch
Iron Sucrose	Equivalent to 20 mg Elemental Iron Fe(III)			
Sodium Hydroxide, NF	q.s. to pH 10.5-11.1			
Water for Injection, USP				

Assessment: Adequate

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(b) (4)

V. List of Outstanding Information Request/Deficiencies:

Outstanding Deficiencies Collation Table
None.

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Wenchun Feng	Kamal Tiwari	2/10/2020	IR	TBD
2	Wenchun Feng	Kamal Tiwari	5/5/2020	CR Minor	Approve
3	Allison Aldridge	Rose Xu	7/9/2021	CR Minor	Approve
4	Allison Aldridge	Rose Xu	3/2/2022	Adequate	Approve
4	Allison Aldridge	Rose Xu	6/15/2022	IR	Approve
4	Allison Aldridge	Rose Xu	1/11/2023	Adequate	Approve

Allison Aldridge

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Date: 1/17/2023 05:55:16PM
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Vidya Pai

Digitally signed by Vidya Pai
Date: 1/17/2023 05:52:29PM
GUID: 53b581d20000464509a65e37ec9ad4a2

FDA U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☐ Complete Response-Minor
☒ Complete Response-Major
☐ Complete Response-Major-Facilities Only

FDA U.S. FOOD & DRUG ADMINISTRATION

ANDA #212340
Assessment #1

Drug Product Name	Iron Sucrose
Dosage Form	Injection
Strength	50 mg/2.5 mL, 100 mg/5 mL, 200 mg/10 mL
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Sandoz Inc.
US agent, if applicable	Gregory Seitz

Submission(s) Assessed	Document Date	Discipline(s) Affected
New ANDA (0001)	08/28/2019	All
Amendment (Response to Labeling DRL)* (0002)	10/31/2019	Labeling
Amendment (Response to BE DRL) (0006)	04/16/2020	BE/DP
Amendment (Response to Quality IR) (0007)	04/24/2020	DP
* Scanned for quality information		

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
DMF Team	Keduo Qian	Deborah Johnson
Drug Substance	Dahui Liu	Yiwei Li
Drug Product	Dahui Liu	Yiwei Li
Manufacturing	Wenchun Feng	Kamal Tiwari
Microbiology	Valerie Huse	Marla Stevens Riley
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Temitope Oriola	
Application Technical Lead	Yiwei Li	
Laboratory (OTR)	N/A	
Environmental*	N/A	
*Categorical exclusion per 21 CFR 25.31 (a)		

U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II	(b) (4)	Iron Sucrose (non-sterile bulk drug substance)	Inadequate -Major	02/26/2020	Reviewed by K. Qian
	III		(b) (4)	N/A		
	III			N/A		
	III			Adequate	01/06/2020	Reviewed by V. Huse
	III			N/A		

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description
NDA	21135	RLD: Venofer® (Iron sucrose Injection, USP) by Luitpold Pharmaceuticals Inc. approved 20-MAR-2005.

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

ABBREVIATED EXECUTIVE SUMMARY (CR ONLY)

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Major

The application is not recommended for approval due to quality related deficiencies summarized in Section II. OPQ recommends issuing a Complete Response Letter – **Major**.

II. QUALITY ASSESSMENT OVERVIEW

A. Drug Substance: Inadequate-Major

1. Primary Justification:

The drug substance deficiencies have been classified as MAJOR because submission of additional physical and or chemical characterization data is needed to demonstrate structure, form or drug substance sameness as noted in Appendix A, Section A(1)(e) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). This data, in FDA's judgement, will require thorough evaluation and potentially affect other aspects of the application and related conclusions.

(b) (4)

[redacted]

Drug Product: Inadequate-Minor

(b) (4)

[redacted]

Labeling: Adequate

No labeling issues were found.

B. Manufacturing: Inadequate-Minor

(b) (4)

[redacted]

(b) (4)

[redacted]

C. Biopharmaceutics: N/A

D. Microbiology: **Inadequate-Major**

1. Primary Justification:

The microbiology deficiencies have been classified as MAJOR because media fill process simulation data supporting the use of the appropriate filling line/machine for your aseptically filled drug product was not provided as noted in Appendix A, Section A(4)(d) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). This information is required to support drug product sterility assurance. Upon receipt, in FDA's judgement, the review of this information will require substantial expenditure of FDA resources

(b) (4)

[redacted]

E. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies: None

2. Drug Substance Deficiencies

1. (b) (4)

[redacted]

2. (b) (4)

a.

b.

3.

3. Drug Product Deficiencies

1. (b) (4)

a. (b) (4)

b.

c.

d.

e.

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8. (b) (4)

9. (b) (4)

10. (b) (4)

a. (b) (4)

b.

4. Labeling Deficiencies: None

5. Manufacturing Deficiencies

1. (b) (4)

2. (b) (4)

a. (b) (4)

b.

c. (b) (4)

d.

3. (b) (4)

6. Biopharmaceutics Deficiencies: N/A

7. Microbiology Deficiencies

1. (b) (4)

2. (b) (4)

3. (b) (4)

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8. **Other Deficiencies: N/A**

Application Technical Lead Name and Date:

Yiwei Li, Ph. D., OLDP/DLBPI/Branch II, 05/29/2020

Yiwei Li

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER I: DRUG SUBSTANCE

IQA ANDA Assessment Guide Reference

Drug Substance Name	Iron (III) Hydroxide Sucrose Complex
ANDA Number	212340
Applicant Name	Sandoz Inc.
Assessment Cycle Number	1
DMF Number (If Applicable)	(b) (4)
DMF Status	Inadequate - Major
DMF Holder	(b) (4)

Assessment Recommendation: **Inadequate - Major**

Theme:

☐ N/A	☐ Other (Requires Division Director Approval)
☒ DMF	☐ Due to Consult
☐ New DS Batch	

Justification: *view justification statements found at:* **Justification Statements**

The drug substance deficiencies have been classified as MAJOR because submission of additional physical and or chemical characterization data is needed to demonstrate structure, form or drug substance sameness as noted in Appendix A, Section A(1)(e) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). This data, in FDA's judgement, will require thorough evaluation and potentially affect other aspects of the application and related conclusions.

Assessment Summary:

(b) (4).

There is no monograph exists. The referenced DMF (b) (4) is last reviewed by Qian, Keduo on 02/26/2020 and found inadequate. The drug substance section is inadequate/major due to inadequate/major DMF. In addition, minor deficiencies are identified in specification.

List Submissions being assessed (*Table*):

Document(s) Assessed	Date Received
Original submission, seq.#0001	8/28/2019
Amendment, seq. # 0002	10/31/2019

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

Concise Description of Outstanding Issues: The section is inadequate due to inadequate DMF and minor deficiencies in specification.

Select Number of Approved Comparability Protocols: 0

S.1 GENERAL INFORMATION

Generic Name	Iron Sucrose
Chemical Name(s)	Iron Sucrose – Iron Saccharate – Sucrose, Iron complex
Other Name(s)	Iron (III) – hydroxide sucrose complex
CAS Number	8047-67-4
Structure	Not Known Structure
Molecular Formula	$[Na_2Fe_5O_8 (OH)\cdot 3(H_2O)]_n \cdot m(C_{12}H_{22}O_{11})$
Molecular Weight	34000 – 60000 Da

Physical Appearance[1]	Homogenous brown-dark powder; Hygroscopic

(b) (4)

Assessment (Review #1): *Adequate*

(b) (4)

Deficiency (Review #1):

(b) (4)

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Assessment: N/A

Lifecycle Management Considerations

N/A

DRUG SUBSTANCE LIST OF DEFICIENCIES

1. (b) (4)

2. (b) (4)

   a. (b) (4)

   b. (b) (4)

3. (b) (4).

Primary Drug Substance Assessor Name and Date: Dahui Liu, Ph.D. 1/30/2020

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

Yiwei Li, Ph. D., OLDP/DLBPI/Branch II, (CR1) 02/12/2020

CHAPTER II: DRUG PRODUCT

IQA ANDA Assessment Guide Reference

Product Information	Iron Sucrose Injection, USP an iron replacement product, is a brown, sterile, aqueous solution, complex of polynuclear iron (III)-hydroxide in sucrose for intravenous use. Iron Sucrose Injection, USP has a molecular weight of approximately 34,000 to 60,000 Daltons and a proposed structural formula: $[Na_2Fe_5O_8(OH) \cdot 3(H_2O)]_n \cdot m(C_{12}H_{22}O_{11})$ where: n is the degree of iron polymerization and m is the number of sucrose molecules associated with the iron (III)-hydroxide. Each mL contains 20 mg elemental iron as iron sucrose in water for injection. Iron sucrose injection is available in 10 mL single-dose vials (200 mg elemental iron per 10 mL), 5 mL single-dose vials (100 mg elemental iron per 5 mL), and 2.5 mL single-dose vials (50 mg elemental iron per 2.5 mL). The drug product contains approximately 30% sucrose w/v (300 mg/mL) and has a pH of 10.5 to 11.1. The product contains no preservatives. The osmolarity of the injection is 1,250 mOsmol/L. The drug product is supplied sterile in 10 mL, 5 mL, and 2.5 mL single-dose vials. Each 10 mL vial contains 200 mg elemental iron, each 5 mL vial contains 100 mg elemental iron, and each 2.5 mL vial contains 50 mg elemental iron. Store in original carton at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). [see USP Controlled Room Temperature]. Do not freeze. There is USP monograph exists for the drug product.
ANDA Number	212340

Assessment Cycle Number	01
Drug Product (DP) Name / Strength	Iron Sucrose Injection USP, 50 mg/2.5 mL, 100 mg/5 mL and 200 mg/10 mL
Route of Administration	Intravenous
Drug Product Manufacturer	Sandoz Inc..
RLD/RS Information (Brand Name of Product, Applicant)	Venofer/ LUITPOLD PHARMACEUTICALS INC
RLD/RS Number	NDA # 021135
Proposed Indication	Iron Sucrose Injection is indicated for the treatment of iron deficiency anemia in patients with chronic kidney disease (CKD)

Assessment Recommendation: **Inadequate - Minor**

Theme:

☒ N/A	☐ Unacceptable Analytical Methods
☐ Unqualified Impurity	☐ Application Quality
☐ New DP Batch	☐ Pharmaceutical Equivalence
☐ Product Design	☐ Product Safety
☐ Failing Stability Data	☐ Other (Requires Division Director Approval)
☐ Application Completeness	☐ Due to Consult

Justification: *view justification statements found at:* **Justification Statements**

N/A

Assessment Summary:
The drug product is a USP item. The firm provided six months stability data at long term, intermediate, and accelerated conditions. (b) (4) [redacted]. The drug product section is inadequate with minor deficiencies in the comparative physicochemical characterization study, specification, compliance with USP <232/233>/ICH Q3D, container closure system, and stability.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Original submission (Seq. # 0001)	**08/28/2019**
Amendment (Seq. # 0002), labeling	**10/31/2019**

Amendment (Seq. #0007), CCS sample shipment	4/24/2020

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

Concise Description of Outstanding Issues (*List Bullet Points with Key Information and Update as Needed*): The drug product section is inadequate with minor deficiencies in the comparative physicochemical characterization study, specification, compliance with USP <232/233>/ICH Q3D, container closure system, and stability.

Select Number of Approved Comparability Protocols: 0

List Current Quality Endorsement Status:

- *USP monograph for Drug Product and compliance (current USP) – status: Inadequate*
- *Dissolution status: N/A*
- *Elemental impurity compliance with ICH Q3D – status: Inadequate*
- *Number of Comparability protocols included: 0*

P.1 DESCRIPTION AND COMPOSITION

Ingredient	Function	Amount per mL	Amount per vial			% w/v	IIG[1] Limit (Injection)
			50 mg/2.5 mL vial	100 mg/5.0 mL vial	200 mg/10.0 mL vial		
Iron Sucrose	Active Pharmaceutical Ingredient	20 mg elemental iron	50 mg elemental iron	100 mg elemental iron	200 mg elemental iron	(b) (4)	
Sodium Hydroxide, NF	pH adjustment	q.s. to pH 10.5 – 11.1	q.s. to pH 10.5-11.1				
Water for Injection, USP			(b) (4)				

(b) (4)

(b) (4)

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REGIONAL INFORMATION

Environmental

Assessment: N/A

Methods Validation or Verification Package

Assessment: N/A

Comparability Protocols

Assessment: N/A

Lifecycle Management Considerations

N/A

DRUG PRODUCT LIST OF DEFICIENCIES

1. [redacted] (b) (4)

a. [redacted] (b) (4)

b.

c.

d.

e.

f.

2 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

(b) (4)

8. (b) (4)

9. (b) (4)

10. (b) (4)

a. (b) (4)

b.

11. (b) (4)

(b) (4)

Primary Drug Product Assessor Name and Date: Dahui Liu, Ph.D., 2/4/2020, 5/6/2020

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

Yiwei Li, Ph. D., OLDP/DLBPI/Branch II, (CR1) 02/12/2020

CHAPTER IV: LABELING

IQA ANDA Assessment Guide Reference

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

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

Is the drug product subject of a USP monograph? ☒ Yes ☐ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☒ Statement not needed

If NO, what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

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:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (MM)	Imprint Code

Send issue to the Labeling assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues:

Issue Description	Issue Reference Number or Link
N/A	N/A

LABELING LIST OF DEFICIENCIES

None

Primary Drug Product Assessor Name and Date: Dahui Liu, Ph.D. 2/4/2020

Secondary Drug Product Assessor Name and Date:

Yiwei Li, Ph. D., OLDP/DLBPI/Branch II, (CR1) 02/12/2020

Dahui Liu

Digitally signed by Dahui Liu
Date: 5/18/2020 02:59:05PM
GUID: 54078879000a1ba887a7e24e53674214

Yiwei Li

Digitally signed by Yiwei Li
Date: 5/20/2020 08:31:49AM
GUID: 5424aeae00c3275e27e75fc260f140b5

M E M O R A N D U M

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

DATE: May 12, 2020

TO: Bing Li, Ph.D.
Acting Director
Office of Bioequivalence (OB)
Office of Generic Drugs (OGD)

FROM: Sripal Reddy Mada, Ph.D.
Pharmacologist
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Amendment - (b) (4)

1. Inspection Summary

The present amendment is to correct FACTS number.

The Office of Study Integrity and Surveillance (OSIS) inspected the in vitro bioequivalence studies (b) (4) conducted at (b) (4)

I did not observe objectionable conditions and did not issue a Form FDA 483 at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

1.1. Recommendation

Based on my review of the inspectional findings, I conclude the data from the audited studies are reliable to support a regulatory decision.

[redacted] (b) (4)

5. Conclusion

After review of the inspectional findings, I conclude that data from the audited studies are reliable.

Studies using similar methods conducted till the end of the current surveillance interval should be considered reliable without an inspection.

Final Classification:

NAI - [redacted] (b) (4)

cc: OTS/OSIS/Kassim/Mitchell/Fenty-Stewart/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDSI/Cho/Choi/Skelly/Au/Mada

Draft: SRM 05/12/2020
Edit: YMC 05/12/2020; SC 05/12/2020
ECMS:http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f881cf53ce

OSIS File: [redacted] (b) (4)
BE 8708 (ANDA 212340)

FACTS: 11954748

Sripal R. Mada -S

Digitally signed by Sripal R. Mada -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sripal R. Mada -S, 0.9.2342.19200300.100.1.1=1300438711
Date: 2020.05.12 12:17:07 -04'00'

Sripal Reddy Mada, Ph.D.

Young M. Choi -S

Digitally signed by Young M. Choi -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Young M. Choi -S, 0.9.2342.19200300.100.1.1=1300119993
Date: 2020.05.12 12:20:08 -04'00'

Young Moon Choi, Ph.D.

Seongeun Cho -S

Digitally signed by Seongeun Cho -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Seongeun Cho -S, 0.9.2342.19200300.100.1.1=2000336978
Date: 2020.05.12 12:58:16 -04'00'

Seongeun (Julia) Cho, Ph.D.

MANUFACTURING INTEGRATED ASSESSMENT

Application ID	ANDA 212340
Drug Product Name	Iron Sucrose Injection, USP Eq. 20 mg base/mL
Strengths	50 mg/2.5 mL, 100 mg/5 mL, 200 mg/10 mL
Dosage Form	Injection
Administration Route	Intravenous
Indication	Iron sucrose injection is an iron replacement product indicated for the treatment of iron deficiency anemia in patients with chronic kidney disease (CKD).
Applicant Name	Sandoz Inc.
RLD Number	N021135

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate

Process Assessment Recommendation: Inadequate - Minor

Assessment Summary:
DP manufacturer, [redacted] (b) (4) is PAI for SVS profile class, with NAI outcome and no 483 observation. [redacted] (b) (4) Based on inspectional history and acceptable profile class, recommend approval. DS manufacturer, [redacted] (b) (4), PAI is completed and no 483 was issued, recommend approval.

Iron Sucrose Injection has three strengths (50 mg/2.5 mL, 100 mg/5 mL, and 200 mg/10 mL). Batch formula includes the API (iron sucrose), excipients (sodium hydroxide and water), [redacted] (b) (4) .
Manufacturing process involves [redacted] (b) (4)

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
Original (1)	8/28/2019

Highlight Key Issues from Last Cycle and Their Resolution:
1. [redacted] (b) (4)
2.

Applicant did not respond to DRL before QDD, therefore there is no resolution to these key issues.

Concise Description of Outstanding Issues (List bullet points with key information and update as needed):

1. (b) (4)
2.

List Number of Comparability Protocols:

None

1. Lifecycle Management Considerations

Post-approval inspection?	No
Lifecycle considerations	No

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
(b) (4)			Approve - Based on PAI
			Approve - Based on Previous History
			Approve - Based on Previous History
			No Evaluation Necessary

II. (b) (4)

1. Batch Formula

2. **Batch Formula of Iron Sucrose Injection, USP 20mg/mL (50mg/2.5mL)**

Proposed Ingredient	(b) (4)	Amount per mL	% w/v	Theoretical Quantity for ANDA Batch	Theoretical Quantity for Proposed Commercial Batch
Iron Sucrose		Equivalent to 20 mg Elemental Iron Fe(III)			
Sodium Hydroxide, NF		q.s. to pH 10.5-11.1			
Water for Injection, USP					

3. **Batch formula of Iron Sucrose Injection, USP 20mg/mL (100mg/5mL)**

Proposed Ingredient	(b) (4)	Amount per mL	% w/v	Theoretical Quantity for ANDA Batch	Theoretical Quantity for Proposed Commercial Batch
				Batch Size	
Iron Sucrose		Equivalent to 20 mg Elemental Iron Fe(III)			
Sodium Hydroxide, NF		q.s. to pH 10.5-11.1			
Water for Injection, USP					

4. **Batch formula of Iron Sucrose Injection, USP 20mg/mL (200mg/10mL)**

Proposed Ingredient	Amount per mL	% w/v	Theoretical Quantity for ANDA Batch	Theoretical Quantity for Proposed Commercial Batch
Iron Sucrose	Equivalent to 20 mg Elemental Iron Fe(III)			
Sodium Hydroxide, NF	q.s. to pH 10.5-11.1			
Water for Injection, USP				

(b) (4)

Assessment: Adequate

(b) (4)

2. *Commercial Process Flow Diagram*

17 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

(b) (4)

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Wenchun Feng	Kamal Tiwari	2/10/2020	IR	TBD
2	Wenchun Feng	Kamal Tiwari	5/5/2020	CR Minor	Approve
Choose an item.			Click to enter a date.	Choose an item.	Choose an item.

Wenchun Feng

Digitally signed by Wenchun Feng
Date: 5/05/2020 12:44:50PM
GUID: 5c3e49dc00b031b507a3645e49842100

Kamal Tiwari

Digitally signed by Kamal Tiwari
Date: 5/05/2020 12:54:02PM
GUID: 508da7040002897e4750ca8cb60b8dc8

MEMORANDUM

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

DATE: April 7, 2020

TO: Bing Li, Ph.D.
Acting Director
Office of Bioequivalence (OB)
Office of Generic Drugs (OGD)

FROM: Sripal Reddy Mada, Ph.D.
Pharmacologist
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: [redacted] (b) (4)

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) inspected the in vitro bioequivalence studies [redacted] (b) (4) conducted at [redacted] (b) (4).

I did not observe objectionable conditions and did not issue a Form FDA 483 at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

1.1. Recommendation

Based on my review of the inspectional findings, I conclude the data from the audited studies are reliable to support a regulatory decision.

2. Inspected Studies

[redacted] (b) (4)

5. Conclusion

After review of the inspectional findings, I conclude that data from the audited studies are reliable.

Studies using similar methods conducted till the end of the current surveillance interval should be considered reliable without an inspection.

Final Classification:

NAI – (b) (4)

cc: OTS/OSIS/Kassim/Mitchell/Fenty-Stewart/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDSI/Cho/Choi/Skelly/Au/Mada

Draft: SRM 04/06/2020
Edit: YMC 04/07/2020; SC 04/07/2020

ECMS:http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f881cf53ce

OSIS File: [redacted] (b) (4)
BE 8708 (ANDA 212340)

FACTS: 11955748

Sripal R. Mada -S
Digitally signed by Sripal R. Mada -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sripal R. Mada -S, 0.9.2342.19200300.100.1.1=1300438711
Date: 2020.04.07 14:36:40 -04'00'

Sripal Reddy Mada, Ph.D.

Young M. Choi -S
Digitally signed by Young M. Choi -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Young M. Choi -S, 0.9.2342.19200300.100.1.1=1300119993
Date: 2020.04.07 14:40:29 -04'00'

Young Moon Choi, Ph.D.

Seongeun Cho -S
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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Seongeun Cho -S, 0.9.2342.19200300.100.1.1=2000336978
Date: 2020.04.07 15:27:03 -04'00'

Seongeun (Julia) Cho, Ph.D.

M E M O R A N D U M

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

DATE: February 13, 2020

TO: Bing Li, Ph.D.
Acting Director
Office of Bioequivalence (OB)
Office of Generic Drugs (OGD)

John Leighton, M.D.
Director
Division of Hematology, Oncology, Toxicology (DHOT)
Office of New Drugs (OND)

FROM: Sripal Reddy Mada, Ph.D.
Pharmacologist
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

Melkamu Getie-Kebtie, Ph.D., R.Ph.
Pharmacologist
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: John A. Kadavil, Ph.D.
Deputy Director
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Amended EIR Review** - Surveillance inspection of [redacted] (b) (4)

1. Inspection Summary

This amended review is being submitted to correct a typographical error for the study conduct dates [redacted] (b) (4) that was observed in the original review.

The Office of Study Integrity and Surveillance (OSIS) inspected the analytical portions of studies [redacted] (b) (4) conducted at [redacted] (b) (4)

We did not observe objectionable conditions and did not issue a Form FDA 483 at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

1.1. Recommendation

Based on our review of the inspectional findings, we conclude the data from the audited studies are reliable to support a regulatory decision.

[redacted] (b) (4)

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[redacted] (b) (4)

5. Conclusion

After review of the inspectional findings, we conclude that data from the audited studies are reliable. In addition, data from studies RFR-P5-709 (TAS) and RFR-P5-709 (TTS) not audited but submitted to a pending application ANDA 212430 (**Attachment 1**) are reliable for Agency review.

Studies using similar methods conducted between the previous inspection (July 2017) and the end of the current surveillance interval should be considered reliable without an inspection.

Final Classification:

NAI – [redacted] (b) (4)

cc: OTS/OSIS/Kassim/Mitchell/Fenty-Stewart/Taylor/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDSI/Cho/Kadavil/Choi/Skelly/Au/Getie-Kebtie/Mada
ORA/OMPTO/OBIMO/FDAInternational BIMO@fda.hhs.gov
Draft: SRM 2/3/2020
Edit: YMC 2/3/2020; JAK 2/12/2020

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/[redacted] (b) (4)

OSIS File: [redacted] (b) (4)
BE 8708 (ANDA 212340)

FACTS: [redacted] (b) (4)

Sripal R. Mada -S
Digitally signed by Sripal R. Mada -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sripal R. Mada -S, 0.9.2342.19200300.100.1.1=1300438711
Date: 2020.02.13 18:47:27 -05'00'

Sripal Mada, Ph.D.

Melkamu Getie Kebtie -S
Digitally signed by Melkamu Getie Kebtie -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0013219608, cn=Melkamu Getie Kebtie -S
Date: 2020.02.13 19:58:42 -05'00'

Melkamu Getie-Kebtie, R.Ph., Ph.D.

Young M. Choi -S
Digitally signed by Young M. Choi -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Young M. Choi -S, 0.9.2342.19200300.100.1.1=1300119993
Date: 2020.02.13 21:28:24 -05'00'

Young Moon Choi, Ph.D.

John A. Kadavil -S
Digitally signed by John A. Kadavil -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300217653, cn=John A. Kadavil -S
Date: 2020.02.14 12:15:13 -05'00'

John A. Kadavil, Ph.D.

Attachment 1
Studies not audited but submitted to pending applications

Application #	Study #	Study Type	Drug Name	Dates of conduct
ANDA 212340	RFR-P5-709 (TAS) (Transferrin Bound Iron)	In vivo	Iron Sucrose 100 mg/5 mL Intravenous Injection	[redacted] (b) (4)
ANDA 212340	RFR-P5-709 (TTS) (Total Iron)	In vivo	Iron Sucrose 100 mg/5 mL Intravenous Injection	

MEMORANDUM

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

DATE: November 20, 2019

TO: Bing Li, Ph.D.
Acting Director
Office of Bioequivalence (OB)
Office of Generic Drugs (OGD)

John Leighton, M.D.
Director
Division of Hematology, Oncology, Toxicology (DHOT)
Office of New Drugs (OND)

FROM: Sripal Reddy Mada, Ph.D.
Pharmacologist
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

Melkamu Getie-Kebtie, Ph.D., R.Ph.
Pharmacologist
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: John A. Kadavil, Ph.D.
Deputy Director
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Surveillance inspection of (b) (4)

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) inspected the analytical portions of (b) (4)

conducted at (b) (4)

We did not observe objectionable conditions and did not issue a Form FDA 483 at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

2 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

[redacted] (b) (4)

5. Conclusion

After review of the inspectional findings, we conclude that data from the audited studies are reliable. In addition, data from studies RFR-P5-709 (TAS) and RFR-P5-709 (TTS) not audited but submitted to a pending application ANDA 212430 (**Attachment 1**) are reliable for Agency review.

Studies using similar methods conducted between the previous inspection (July 2017) and the end of the current surveillance interval should be considered reliable without an inspection.

Final Classification:

NAI - [redacted] (b) (4)

cc: OTS/OSIS/Kassim/Mitchell/Fenty-Stewart/Taylor/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas

OTS/OSIS/DGDSI/Cho/Kadavil/Choi/Skelly/Au/Getie-Kebtie/Mada
ORA/OMPTO/OBIMO/FDAInternational BIMO@fda.hhs.gov

Draft: SRM 10/30/2019, 11/19/2019
Edit: MGK 11/05/2019, 11/12/2019; YMC 11/07/2019, 11/19/2019;
JAK 11/19/2019, 11/20/2019

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and
Surveillance/INSPECTIONS/BE [redacted] (b) (4)

OSIS File: [redacted] (b) (4)

BE 8708 (ANDA 212430)

FACTS: [redacted] (b) (4)

Sripal R. Mada -S
Digitally signed by Sripal R. Mada -S
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Date: 2019.11.20 12:45:31 -05'00'

Sripal Mada, Ph.D.

Melkamu Getie Kebtie -S
Digitally signed by Melkamu Getie Kebtie -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0013219608, cn=Melkamu Getie Kebtie -S
Date: 2019.11.20 12:52:11 -05'00'

Melkamu Getie-Kebtie, R.Ph., Ph.D.

Young M. Choi -S
Digitally signed by Young M. Choi -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Young M. Choi -S, 0.9.2342.19200300.100.1.1=1300119993
Date: 2019.11.20 12:55:39 -05'00'

Young Moon Choi, Ph.D.

John A. Kadavil -S
Digitally signed by John A. Kadavil -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300217653, cn=John A. Kadavil -S
Date: 2019.11.20 13:00:02 -05'00'

John A. Kadavil, Ph.D.

Attachment 1
Studies not audited but submitted to pending applications

Application #	Study #	Study Type	Drug Name	Dates of conduct
ANDA 212430	RFR-P5-709 (TAS) (Transferrin Bound Iron)	In vivo	Iron Sucrose 100 mg/5 mL Intravenous Injection	08/24/2018 - 11/07/2018
ANDA 212430	RFR-P5-709 (TTS) (Total Iron)	In vivo	Iron Sucrose 100 mg/5 mL Intravenous Injection	08/22/2018 - 11/06/2018

10 Pages have been withheld in full as b4 immediately following this page

MEMORANDUM

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

DATE: 10/1/2019

TO: Office of Bioequivalence
Office of Generic Drugs

FROM: Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: ANDA 212340

The Division of Generic Drug Bioequivalence Evaluation (DGDBE) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

The Office of Regulatory Affairs (ORA) inspected the site in June 2019, which falls within the surveillance interval. The inspection was conducted under the following submission: NDA 210858.

The final classification for the inspection was No Action Indicated (NAI).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	Altasciences	1200 Beaumont Avenue, Mount-Royal, Quebec, Canada

Folaremi Adeyemo

Digitally signed by Folaremi Adeyemo
DN: cn=Folaremi Adeyemo, o, ou, email=folaremi.adeyemo@fda.hhs.gov, c=US
Date: 2019.10.01 08:47:58 -04'00'

Timely Consults and Early IR Checklist for Type II API DMFs

Result: TCIR-NAI

ANDA#: 212340

Drug Product: IRON SUCROSE INJECTION

DMF#: (b) (4)

DMF Subject (API name): IRON SUCROSE

Note: If the DMF is for a mixture of the API and excipient(s) (e.g. stabilizer, buffer), email DMF OGD Mailbox (DMFOGD@fda.hhs.gov) and include the URL to the project; example "this TCIR is for an API excipient mixture".). Note to reviewer: Do not archive the TCIR document as changes may need to be made.

1. **Are there any secondary DMFs referenced by this DMF? ☐Yes ☒No**
   If yes, fill in the following table.

Secondary DMF #	Subject of the DMF	Intermediate/Starting material?

Note: If the secondary DMF is for a regulatory starting material, a review of the secondary DMF may not be needed.

2. **Are there any intermediate facilities listed in the 356h? ☐Yes ☒No**
   If yes, determine if the intermediate facility is critical.

Facility Name and Address	FEI/DUNS	Intermediate critical (Y/N)	Justification*

*** If an intermediate facility is identified, please select justification(s) from the following:**

1. **The intermediate is not separated by an adequate number of steps from the final API. The risk to DS quality cannot be adequately mitigated through the intermediate specification and thereby the facility warrants evaluation.**

2. **The intermediate route of synthesis involves unusual or complex chemistry which presents a risk to DS quality that cannot be adequately mitigated through the intermediate specification.**

3. The drug substance is very complex, and the intermediate route of synthesis introduces the most critical structural features and the risk to DS quality cannot be adequately mitigated through the intermediate specification.

4. Intermediate is not deemed critical because the criteria above do not apply.

5. The intermediate would be deemed critical if new, but the current intermediate facility was a pre- existing facility and was not evaluated for other applications.

3. Does the Type II API DMF list any manufacturing facilities, intermediate facilities, or testing facilities for routine release or stability testing that are **not listed in the facility profile and/or on the 356h** form for the referencing ANDA? ☐Yes ☒No

If yes, include the information identifying each facility and its function below:

Facility Name and Address[#]	Function[$]	Justification if Intermediate facility*	FEI/DUNS[#]

* If an intermediate facility is identified, please select justification(s) from the following:

1. The intermediate is not separated by an adequate number of steps from the final API. The risk to DS quality cannot be adequately mitigated through the intermediate specification and thereby the facility warrants evaluation.

2. The intermediate route of synthesis involves unusual or complex chemistry which presents a risk to DS quality that cannot be adequately mitigated through the intermediate specification.

3. The drug substance is very complex, and the intermediate route of synthesis introduces the most critical structural features and the risk to DS quality cannot be adequately mitigated through the intermediate specification.

4. Intermediate is not deemed critical because the criteria above do not apply.

5. The intermediate would be deemed critical if new, but the current intermediate facility was a pre- existing facility and was not evaluated for other applications.

[$] Facility function codes for hidden and critical intermediate facilities:

CSN: Non-Sterile API by Chemical Synthesis
CSS: Sterile API by Chemical Synthesis
CSP: Chemical Sterilization
LCP: Laboratory, Chemical/Physical Testing
LBI: Laboratory, Biological Testing
LMS: Laboratory, Microbiological – Sterility Testing
LMN: Laboratory, Microbiological – Non-Sterility Testing
CXA: Plant/Animal Extraction Purified API
CFN: Non –Sterile API by Fermentation
CFS: Sterile API by Fermentation
CRU: API Non-Sterile/Intermediate

Note: *Add "-Critical Intermediate" to the appropriate manufacturing code if the site manufactures a critical intermediate.*
*#**Note:** Not for FOI boxes (refer to SOP for format) need to be used if the facility information is submitted in a secondary DMF.*

RBPM to include the following comment in the early-IR sent to the applicant:

"Please note that there are manufacturing facility (critical intermediate) that are included in DMF [DMF#] for [API name] that were not included on your form 356h. Please contact your DMF holder to resolve any discrepancies and clarify which DMF related facilities support your application. Please note that a revised 356h form will be required to add any new facilities to your application. The addition of a new facility or new facilities may result in an extension of the performance goal date for your submission."

RBPM to include the following modified comment in the early-IR sent to the applicant if the facility information is submitted in a secondary DMF:

"Please note that there is a manufacturing facility (critical intermediate) that is included in a DMF referenced by [Primary DMF#] for [API name] that was not included on your form 356h. Please contact your DMF holder to resolve any discrepancies and clarify which DMF related facilities support your application. Please note that a revised 356h form will be required to add any new facilities to your application. The addition of a new facility or new facilities may result in an extension of the performance goal date for your submission."

3. Does the DMF include any data (e.g. Ames study or cited literature studies) that requires a pharm/tox consult?
   ☐Yes ☒No

   If yes, prepare the consult and send to DCR in Panorama and enter date sent below.

   Consult form date:

4. After examining the labelling for the drug product:

   Is a DCR consult required to establish the Maximum Daily Dose (MDD)? ☐Yes ☒No

   Is a DCR consult required to establish the product use (i.e. duration and frequency of use, patient population)? ☐Yes ☒No

   The following question applies to drug products indicated for the treatment of cancer.

   Is a consult required to determine if the drug product is indicated for the treatment of advanced cancer in the context of ICH S9? ☐Yes ☒No

   Is a DCR consult required to determine that the drug substance is carcinogenic? ☐Yes ☒No

   If yes to any of the above prepare the appropriate consult and send to DCR in Panorama and enter date sent below.

   Consult form date:

Benjamin Lim

Digitally signed by Benjamin Lim
Date: 9/27/2019 02:19:37PM
GUID: 508da7040002892a7c056659385f70e2

List of Deficiencies for ANDA #212340

A. Drug Substance Deficiencies

B. Drug Product Deficiencies

C. Microbiology Deficiencies

1. (b) (4)

2.

3.

4.

a)

b)

5.

6 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

14. (b) (4)

[redacted]

D. Process Deficiencies

1. (b) (4)

[redacted]

2. (b) (4)

[redacted]

A. (b) (4)

[redacted]

B. (b) (4)

[redacted]

(b) (4)

C. (b) (4)

D. (b) (4)

3. (b) (4)

E. Facilities Deficiencies

F. Biopharmaceutics Deficiencies

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 212340

BIOEQUIVALENCE REVIEW(s)

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	212340	
Drug Product Name	Iron Sucrose Injection [a]	
Strength(s)	EQ 20 mg Iron/mL (EQ 50 mg Iron/2.5 mL, EQ 100 mg Iron/5 mL, and EQ 200 mg Iron/10 mL)	
Applicant Name	Sandoz Inc.	
Applicant Address	100 College Road West, Princeton, NJ 08540	
US Contact Name and US Mailing Address	Gregory Seitz, Head, U.S. Regulatory Affairs Generics 100 College Road West, Princeton, NJ 08540	
US Contact Telephone Number	(b)(6)	
US Contact Fax Number	973-781-3710	
Original Submission Date(s)	08/29/2019 Original	
Submission Date(s) of Amendment(s) Under Review	04/16/2020 Bioequivalence/Response to Discipline Review Letter 12/28/2020 Bioequivalence/Response to Complete Response Letter 08/18/2023 Bioequivalence/Response to Complete Response Letter 06/11/2025 Labeling/Response to Discipline Review Letter [b]	
Primary Reviewer	Ja Hye Myung, Ph.D.	
Secondary Reviewer	Moheb H. Makary, Ph.D.	
Study Number(s)	**RFR-P5-709**	**IRSUS_REP DLS_IVC_V03**
Study Type(s)	Fasting	In Vitro BE (Particle Size Distribution)
Strength(s)	EQ 100 mg Iron/5 mL	EQ 100 mg Iron/5 mL
Clinical Site	Algorithme Pharma Inc.	N/A
Clinical Site Address	1200 Beaumont Ave., Mount-Royal, Quebec, Canada H3P 3P1	N/A
Analytical Site	(b)(4)	
Analytical Site Address		
Office of Study Integrity and Surveillance (OSIS) status	**Backlog, Year 1 and Year 2 ANDAs** ☐ Pending ☐ Complete ☐ N/A	**Post October 1, 2014 ANDAs** ☐ Pending ☐ Pending for Cause Inspection ☒ Complete ☐ N/A
Waiver/Deem Bioequivalent	☒ Granted ☐ Tentatively granted ☐ Not granted ☐ N/A	
QC Dissolution	☐ Pending ☐ Adequate ☐ Inadequate ☒ N/A	

Formulation	☒ **Adequate** ☐ **Inadequate**		
Will Response to CR Result in a Reformulation?	☐ **Possibly** ☐ **No** ☒ **N/A**		
Deficiency Classification	☐ **Major** ☐ **Minor** ☒ **N/A** (the review is adequate)		
Major Deficiency Theme	**N/A**		
Justification for Major Designation	**N/A**		
Overall Review Result	☒ **Adequate** ☐ **Inadequate**		
Product Specific Guidance (PSG) Referenced in Review	☒ **Recommended/Latest Revision Date: Sep 2021** **RLD/RS Number: N021135** ☐ **N/A**		
Revised/New Draft Guidance Generated as Part of Current Review	☐ **YES** ☒ **NO**		
Bioequivalence study tracking/supporting document #	**Study/ test type**	**Strength**	**Review Result**
#1, 6, 9, and 13	**Fasting**	**EQ 100 mg Iron/5 mL**	☒ **Adequate** ☐ **Inadequate**
#1, 6, 9, and 13	**In Vitro (particle size distribution)**	**EQ 100 mg Iron/5 mL**	☒ **Adequate** ☐ **Inadequate**
#1, 6, 9, 13, and 18	**Waivers**	**EQ 50 mg Iron/2.5 mL and EQ 200 mg Iron/10 mL**	☒ **Adequate** ☐ **Inadequate**

[a] As per the Agency's the memorandum to CP Docket Nos. FDA-2016-P-1163 and FDA-2021-P-0893 issued on 07/01/2024, API name has been reverted from "Ferric Oxyhydroxide" to "Iron Sucrose".

[b] As per the discipline review letter (DRL) issued from Labeling review team on 06/05/2025, the applicant submitted their updated composition statement in Module 3.2.P.1. as well as labeling to include sodium chloride as [redacted] in the Amendment-18 on 06/11/2025.

ADDENDUM TO BIOEQUIVALENCE REVIEW

This is an **addendum** to the bioequivalence (BE) review of ANDA 212340-Amendment-13 finalized on 04/03/2024.[1] The purpose of this addendum is to evaluate the formulation sameness between the reference listed drug (RLD) and test products, based on the updated formulation information in Amendment-18 submitted on 06/11/2025 in response to the Discipline Review Letter (DRL) issued from Labeling on 06/05/2025.[2]

The agency has identified (b)(4) as an excipient in the RLD.[3] Per DMF (b)(4) used for current ANDA 212340,[4,5] (b)(4)

(b)(4)

Here we summarize the BE review history as following. In the BE addendum to ANDA 212340-Amendment-9-Addendum,[6] it was considered that the applicant's test formulation for ANDA 212340 was not qualitatively (Q1)/quantitively (Q2) the same as the RLD. The information was communicated to the applicant via the Complete Response Letter (CRL) issued on 04/17/2023.[7]

Per the applicant's CRL responses in Amendment-13 submitted on 08/18/2023, the applicant identified (b)(4)

(b)(4)

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[1] DocuBridge, ANDA 212340, #0018(18) 06/11/2025, Module 1.2 Cover Letters; \\CDSESUB1\EVSPROD\anda212340\0018\m1\us\12-cover-letters\cover-letter.pdf

[2] Panorama, ANDA-212340-ORIG-1-AMEND-13, Labeling Discipline Review, Send DRL, 06/05/2025; https://panorama.fda.gov/task/view?ID=6841de10001d6a7afa95d680c75153a3

[3] Panorama, ANDA-212340-ORIG-1-AMEND-9, Drug Product Quality Review, Reviewer: Dahui Liu, A212340 Drug Product R02b-IQ.docx; https://panorama.fda.gov/task/view?ID=5fecbfda00de02508b9c590a6ba7295f

[4] Panorama, ANDA-212340-ORIG-1-AMEND-9, Drug Product Quality Review, Reviewer: Dahui Liu, A212340 Drug Product R02b-IQ.docx; https://panorama.fda.gov/task/view?ID=5fecbfda00de02508b9c590a6ba7295f

[5] R:\OGDS11\DIVISION\BIO\BIO3\Email Communications\ANDA 212340 Iron Sucrose Injection\A212340_email communication with OPQ_NaCl in drug product.pdf

[6] Panorama, ANDA-212340-ORIG-1-AMEND-9, Bioequivalence Discipline Review, 02/24/2023, A212340N000DB-Review01-Addendum12282020.pdf; https://panorama.fda.gov/task/view?ID=5fecbfda00de004de0a05eab1f8f1710

[7] Panorama, ANDA-212340-ORIG-1-AMEND-9, Final Decision, 04/17/2023; https://panorama.fda.gov/task/view?ID=5fecbfda00de041c45174061adc0ead7

[8] Panorama, ANDA-212340-ORIG-1-AMEND-13, Drug Product Quality Review; https://panorama.fda.gov/task/view?ID=64e5746f00586d4edd75f1907c2453fc

212340-Amendment-13,[9] the internal Q1/Q2 evaluation indicated that the test product formulation was acceptable. At the time of Amendment-13 review, [redacted] was not yet determined to be an excipient in the RLD and this ANDA. Based on internal communication with OGDP, no BE deficiency for this ANDA was issued at that stage.

On 07/01/2024, the Agency's memorandum to Citizen Petition Docket Nos. FDA-2016-P-1163 and FDA-2021-P-0893 was issued.[10] The memorandum stated that the Center for Drug Evaluation and Research (CDER) "*is reevaluating its determination that the active ingredient of the iron products subject to the May 26, 2021, Citizen Petition response is ferric oxyhydroxide. While CDER's reevaluation is ongoing, CDER is accepting the active ingredient names as approved prior to the May 26, 2021, Citizen Petition response for all iron products subject to the May 26, 2021, Citizen Petition response...*" In addition, the product specific guidance (PSG) on Ferric Oxyhydroxide referring to NDA 021135 has been revised.[11] It is scheduled to be posted on the public domain on the same date the responses to the following pending Citizen Petitions are issued: Docket No. FDA-2021-P-0893 and Docket No. FDA-2005-P-0319.[12]

On 06/05/2025, the Labeling review team sent the following deficiency via Discipline Review Letter (DRL):[13] [redacted]

(b)(4)

Per the applicant's DRL responses in Amendment-19 submitted on 06/17/2025,[15] the current applicant consulted with the DMF [redacted] holder and revised the statement in Section 11 of the prescribing information and on the carton/container labeling: "*The drug*

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[9] Panorama, ANDA-212340-ORIG-1-AMEND-13, Bioequivalence Discipline Review, 04/03/2024, A212340N000DB-Review02-AmendCRLResponse08182023.pdf; https://panorama.fda.gov/task/view?ID=64e5746f00586b5238def68c0399ba4d

[10] https://www.regulations.gov/document/FDA-2016-P-1163-0101; https://www.regulations.gov/document/FDA-2021-P-0893-0079

[11] Panorama, CC #63047457, Iron Sucrose Intravenous Injectable NDA 021135 Revision PSG; https://panorama.fda.gov/project/view?ID=67d2ca0900dc0ffc15ef032499da2331

[12] The previous bioequivalence reviews, dated 02/24/2023 and 04/03/2024, provide detailed information about the previous Citizen Petition response dated May 26, 2021, the pending Petition and Petition for Stay (Docket No. FDA-2021-P-0893) and an additional pending Citizen Petition related to Venofer (Docket No. FDA-2005-P-0319).

[13] Panorama, ANDA-212340-ORIG-1-AMEND-13, Labeling Discipline Review, Send DRL, 06/05/2025; https://panorama.fda.gov/task/view?ID=6841de10001d6a7afa95d680c75153a3

[14] Panorama, ANDA-212340-ORIG-1-AMEND-13, Labeling Discipline Review, Send DRL, 06/05/2025; https://panorama.fda.gov/task/view?ID=6841de10001d6a7afa95d680c75153a3

[15] DocuBridge, ANDA 212340, #0019(19) 06/17/2025, Module 1.2. Cover Letters, Cover Letter-0019-20250617-Labeling Amendment.pdf; \\CDSESUB1\EVSPROD\anda212340\0019\m1\us\12-cover-letters\cover-letter.pdf

product contains approximately 30% sucrose w/v (300 mg/mL) and sodium chloride for tonicity."[16] In addition, the applicant removed [redacted] (b)(4)

(b)(4)

Revised composition table of the drug product (i.e., Iron Sucrose Injection, 100 mg/5 mL) in Amendment-18 (submission date: 06/11/2025)[19]

Ingredient	Function	Amount per mL	Amount per vial	% w/v	IIG[1] Limit (Injection)
Iron Sucrose	Active Pharmaceutical Ingredient	20 mg elemental iron	(b)(4)		
Sodium Hydroxide, NF	pH Adjustment	q.s. to pH 10.5 – 11.1			
(b)(4)					

The composition of the RLD formulation table is shown below.

[16] DocuBridge, ANDA 212340, #0019(19) 06/17/2025, Module 1.14.1.3. Draft Labeling Text, Draft Labeling Text.pdf; \\CDSESUB1\EVSPROD\anda212340\0019\m1\us\114-labeling\draft\labeling\draft-labeling-text-pdf.pdf

[17] DocuBridge, ANDA 212340, #0018(18) 06/11/2025, Module 1.1.2. FDA Form 356h-0018-20250611-Labeling Amendment; \\CDSESUB1\EVSPROD\anda212340\0018\m1\us\11-forms\356h.pdf

[18] DocuBridge, ANDA 212340, #0013(13) 08/18/2023, Module 3.2.P.1 Description and Composition of the Drug Product; \\CDSESUB1\EVSPROD\anda212340\0013\m3\32-body-data\32p-drug-prod\iron-sucrose-injection-rafarm-sa\32p1-desc-comp\fp-description-and-composition.pdf

[19] DocuBridge, ANDA 212340, #0018(18) 06/11/2025, Module 3.2.P.1 Description and Composition of the Drug Product; \\CDSESUB1\EVSPROD\anda212340\0018\m3\32-body-data\32p-drug-prod\iron-sucrose-injection-rafarm-sa\32p1-desc-comp\fp-description-and-composition.pdf

RLD Formulation (Not to be released under FOIA, [20]

(b)(4)

Qualitative and Quantitative Comparison between Test and RLD formulations (Not to be released under FOIA)

(b)(4)

As per the abovementioned memorandum to CP Docket No. FDA-2016-P-1163, the changed nomenclature of API name (i.e., iron sucrose) is acceptable. The DMF holder adequately identifies and characterizes as an excipient that

(b)(4)

[22] As stated in the CC #139879 review[23] and BE review of original A212340 submission[24], the internal Q1/Q2 evaluation indicated that the test product formulation is acceptable since the proposed test formulation is Q1/Q2 the same as the RLD with respect to inactive ingredients.

[20] DocuBridge, NDA 021135, #0280(821) 12/18/2024, Module 3.2.P.3.3. Description of Manufacturing Process and Process Controls, formulation-batch-record-ar-mbr-1578.pdf; \\CDSESUB1\EVSPROD\nda021135\0280\m3\32-body-data\32p-drug-prod\venofer-iron-sucrose-inje-20-mgml-injectable-american-regent-inc\32p3-manuf\formulation-batch-record-ar-mbr-1578.pdf

(b)(4)

[22] Panorama, ANDA-212340-ORIG-1-AMEND-13, Drug Product Quality Review; https://panorama.fda.gov/task/view?ID=64e5746f00586d4edd75f1907c2453fc

[23] Panorama, CC #139879, 04/16/2015; https://panorama.fda.gov/project/view?ID=5530eacc00b948a4b026e00c8c5e501e

[24] Panorama, ANDA-212340-ORIG-1, Bioequivalence Discipline Review, A212340N000DB-N08282019.pdf; https://panorama.fda.gov/task/view?ID=5d67e9b9000718fa7680eb2c46e9558b

Based on the DRL issued from Labeling on 06/05/2025, [redacted] is now listed in the Section 11 of the prescribing information and container/carton labeling consistent with 21CFR201.100(b)(5)(iii),[25] which is acceptable per the Labeling Review.[26]

Per previous BE assessments,[27,28] the in vivo fasting BE study (Study #RFR-P5-709) and in vitro particle size distribution (PSD) study (Study #IRSUS_REP DLS_IVC_V03) were deemed acceptable. The formulation of other two strengths of the test product, Iron Sucrose Injections, EQ 50 mg Iron/2.5 mL and EQ 200 mg Iron/10 mL is proportional similar to the formulation of the bio-strength (EQ 100 mg base/5 mL), which was used for in vivo and in vitro BE studies. The waiver requests of in vivo and in vitro BE studies for the test product, Iron Sucrose Injections, EQ 50 mg Iron/2.5 mL and EQ 200 mg Iron/10 mL, are granted.

As a result, the application remains **adequate** from the BE perspective.

The BE letter in this addendum is same as the BE letter for the BE review dated 04/03/2024. It is attached to the end of the current document for reference.

[25] DocuBridge, ANDA 212340, #0018(18) 06/11/2025, Module 1.14.3.1. Nnotated Comparison with Previously Submitted PI; \\CDSESUB1\EVSPROD\anda212340\0018\m1\us\114-labeling\listed-drug\annotated\annotated-comparison-with-previously-submitted-pi.pdf
[26] Panorama, ANDA-212340-ORIG-1-AMEND-13, Labeling Discipline Review; https://panorama.fda.gov/task/view?ID=64e5746f00586b9a604aff557d0adbd4
[27] Panorama, ANDA-212340-ORIGI-1, Bioequivalence Review, Reviewer: Yun Wang (4); https://panorama.fda.gov/task/view?ID=5d67e9b9000718fa7680eb2c46e9558b
[28] Panorama, ANDA-212340-ORIG-1-AMEND-9, Bioequivalence Review, Reviewer: Usha Katragadda; https://panorama.fda.gov/task/view?ID=5fecbfda00de004de0a05eab1f8f1710

NOTE TO REGULATORY PROJECT MANAGER: As of 08/01/2025, there are two policy alerts from OGDP related to Iron Sucrose Injection (Docket # FDA-2005-P-0319 (2005P-0095) and # FDA-2021-P-0893, for Venofer® (ferric oxyhydroxide) Injection (NDA 021135)). OGDP will need to coordinate answering the CP with any approvals or tentative approvals, so please contact the Policy lead as soon as any application is possibly headed for an Approval Action (AP/TA).

The letter in the current bioequivalence addendum review is the same as the letter at the end of the bioequivalence review, which is located in GDRP [GDRP, ANDA-212340-ORIG-1-AMEND-13, Bioequivalence Discipline Review, A212340N000DB-Review02-AmendCRLResponse08182023.pdf, Completed on 04/03/2024].

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	212340
APPLICANT:	Sandoz Inc.
DRUG PRODUCT:	Iron Sucrose Injection, EQ 20 mg Iron/mL (EQ 50 mg Iron/2.5 mL, EQ 100 mg Iron/5 mL, and EQ 200 mg Iron/10 mL)

The Division of Bioequivalence III (DBIII) has completed its review of your submission acknowledged on the cover sheet and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns are raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

April C. Braddy, Ph.D., RAC
Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OUTCOME PAGE

Completed Assignment for 212340 ID: 56929

Reviewer:	Myung, Ja Hye	**Date Completed:**	
Verifier:	,	**Date Verified:**	
Division:	Division of Bioequivalence		
Description:	A212340-Amendment 18-Iron Sucrose Injection, EQ 20 mg Iron/mL (Sandoz)		

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*		
56929	8/18/2023	Parallel2025	Other (Addendum not for error correction) (0.5 per application) [0.5]	0.5	0.5	Edit	Delete

DIVISION OF BIOEQUIVALENCE AMENDMENT REVIEW

ANDA No.	212340	
Drug Product Name	Iron Sucrose Injection [a]	
Strength(s)	EQ 20 mg Iron/mL (EQ 50 mg Iron/2.5 mL, EQ 100 mg Iron/5 mL, and EQ 200 mg Iron/10 mL)	
Applicant Name	Sandoz Inc.	
Applicant Address	100 College Road West, Princeton, NJ 08540	
US Contact Name and US Mailing Address	Gregory Seitz, Director, Regulatory Affairs	
US Contact Telephone Number	(b)(6)	
US Contact Fax Number	973-781-3710	
Original Submission Date(s)	08/29/2019 Original	
Submission Date(s) of Amendment(s) Under Review	04/16/2020 Bioequivalence/Response to Discipline Review Letter 12/28/2020 Bioequivalence/Response to Complete Response Letter 08/18/2023 Bioequivalence/Response to Complete Response Letter	
Primary Reviewer	Ja Hye Myung, Ph.D.	
Secondary Reviewer	Moheb H. Makary, Ph.D.	
Study Number(s)	**RFR-P5-709**	**IRSUS_REP DLS_IVC_V03**
Study Type(s)	Fasting	In Vitro BE (Particle Size Distribution)
Strength(s)	EQ 100 mg Iron/5 mL	EQ 100 mg Iron/5 mL
Clinical Site	Algorithme Pharma Inc.	Not applicable
Clinical Site Address	1200 Beaumont Ave., Mount-Royal, Quebec, Canada H3P 3P1	Not applicable
Analytical Site	(b)(4)	
Analytical Site Address		
Office of Study Integrity and Surveillance (OSIS) status	**Backlog, Year 1 and Year 2 ANDAs** **☐ Pending** **☐ Complete** **☐ N/A**	**Post October 1, 2014 ANDAs** **☐ Pending** **☐ Pending for Cause Inspection** **☒ Complete** **☐ N/A**
Waiver/Deem Bioequivalent	**☒ Granted ☐ Tentatively granted ☐ Not granted ☐ N/A**	
QC Dissolution	**☐ Pending ☐ Adequate ☐ Inadequate ☒ N/A**	
Formulation	**☒ Adequate ☐ Inadequate**	

Will Response to CR Result in a Reformulation?	☐ **Possibly** ☐ **No** ☒ **N/A**		
Deficiency Classification	☐ **Major** ☐ **Minor** ☒ **N/A** (the review is adequate)		
Major Deficiency Theme	**N/A**		
Justification for Major Designation	**N/A**		
Overall Review Result	☒ **Adequate** ☐ **Inadequate**		
Product Specific Guidance (PSG) Referenced in Review	☒ **Recommended/Latest Revision Date: Sep 2021** **RLD/RS Number: N021135** [b] ☐ **N/A**		
Revised/New Draft Guidance Generated as Part of Current Review	☐ **YES** ☒ **NO**		
Bioequivalence study tracking/supporting document #	**Study/ test type**	**Strength**	**Review Result**
#1, 6, 9, and 13	**Fasting**	**EQ 100 mg Iron/5 mL**	☒ **Adequate** ☐ **Inadequate**
#1, 6, 9, and 13	**In Vitro (particle size distribution)**	**EQ 100 mg Iron/5 mL**	☒ **Adequate** ☐ **Inadequate**
#1, 6, 9, and 13	**Waivers**	**EQ 50 mg Iron/2.5 mL and EQ 200 mg Iron/10 mL**	☒ **Adequate** ☐ **Inadequate**

[a] Based on a citizen petition (Docket #FDA-2005-P-0319, see Section 3.3), API name has been changed from "Iron Sucrose" to "Ferric Oxyhydroxide". The old API name "Iron Sucrose" is used in the current assessment since the applicant has used it in the original submission.

[b] There are several different reference drugs that use the active ingredient, ferric oxyhydroxide (e.g., Venofer, Ferrlecit, INFED, [redacted] The current ANDA under review is referencing Venofer® (ferric oxyhydroxide) Injection.

REVIEW OF AN AMENDMENT

1. EXECUTIVE SUMMARY

This is a review of an **amendment** (supporting document #13) dated 08/18/2023,[1] in which the applicant responded to the deficiency communicated in the Complete Response Letter (CRL) dated 04/17/2023.[2]

The formulation of the test product was previously reviewed and determined that the test product was not qualitatively (Q1) and quantitatively (Q2) the same as the reference listed drug (RLD) product in the addendum review dated 02/24/2023.[3] Per discussion with Office of Pharmaceutical Quality (OPQ), a thorough review of NDA 021135 (RLD) and drug master file (DMF) # has identified . Per DMF used for current ANDA 212340, . Thus, the Division of Bioequivalence III (DBIII) issued a major deficiency related to the Q1/Q2 sameness issue in the CRL dated 04/17/2023.

In the current amendment, the applicant identifies the active ingredient, ferric oxyhydroxide with sucrose as an excipient. Although is still not listed in the formulation composition table, based on the updated OPQ review,[4] "*Per our internal review* Therefore, based on the above information, our internal Q1/Q2 evaluation indicates that the test product formulation is acceptable.

Per previous BE assessments,[5,6] the in vivo fasting BE study (Study #RFR-P5-709) and in vitro particle size distribution (PSD) study (Study #IRSUS_REP DLS_IVC_V03) were deemed acceptable. The formulation of other two strengths of the test product, Iron Sucrose Injections, EQ 50 mg Iron/2.5 mL and EQ 200 mg Iron/10 mL is proportional similar to

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[1] DocuBridge, ANDA 212340, #0013(13) 08/18/2023, Module 1.2 Cover Letters; \\CDSESUB1\EVSPROD\anda212340\0013\m1\us\12-cover-letters\cover-letter.pdf

[2] Panorama, ANDA-212340-ORIG-1-AMEND-9, Final Decision, A212340N000DPM-CompleteResponse02.pdf; https://panorama.fda.gov/task/view?ID=5fecbfda00de041c45174061adc0ead7

[3] Panorama, ANDA-212340-ORIG-1-AMEND-9, Bioequivalence Review, A212340N000DB-Review01-Addendum12282020.pdf; https://panorama.fda.gov/task/view?ID=5fecbfda00de004de0a05eab1f8f1710

[4] Panorama, ANDA-212340-ORIG-1-AMEND-13, Drug Product Quality Review; https://panorama.fda.gov/task/view?ID=64e5746f00586d4edd75f1907c2453fc

[5] Panorama, ANDA-212340-ORIGI-1, Bioequivalence Review, Reviewer: Yun Wang (4); https://panorama.fda.gov/task/view?ID=5d67e9b9000718fa7680eb2c46e9558b

[6] Panorama, ANDA-212340-ORIG-1-AMEND-9, Bioequivalence Review, Reviewer: Usha Katragadda; https://panorama.fda.gov/task/view?ID=5fecbfda00de004de0a05eab1f8f1710

the formulation of the bio-strength (EQ 100 mg base/5 mL), which was used for in vivo and in vitro BE studies. The waiver requests of in vivo and in vitro BE studies for the test product, Iron Sucrose Injections, EQ 50 mg Iron/2.5 mL and EQ 200 mg Iron/10 mL, are granted.

The application is **adequate** from the BE perspective. Based on internal communication with Office of Generic Drug Policy (OGDP), no BE deficiency for this ANDA will be issued at this stage.

2. TABLE OF CONTENTS

3. BACKGROUND

- The original application contains the results of a in vivo fasting bioequivalence (BE) study (Study #RFR-P5-709) comparing a test product, Sandoz Inc.'s Iron Sucrose Injection, Eq. 20 mg base/mL, to the corresponding RLD product, American Regent Inc's Venofer® (iron sucrose) Injection, EQ 100 mg Iron/5 mL (EQ 20 mg Iron/mL). The fasting BE study was designed as a single-dose, two-treatment, fourteen-group, parallel study in healthy male and female subjects. The fasting BE study results are summarized in the table below, which fall within the acceptance range of 80.00-125.00%. However, as per the original BE review,[7] the applicant's fasting study is inadequate due to bioanalytical deficiency.

Iron Sucrose USP Injection (No of subjects completed = 200) Dose: 1 x 100 mg Least Squares Geometric Means, Ratio of Means (%), and 90% Confidence Intervals (%)							
Pivotal Fasting Bioequivalence Study (Study No. RFR-P5-709)							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *µg/dl)	5548.15	100	6367.12	100	0.87	81.92	92.68
AUC∞ (hr *µg/dl)	5983.54	85+	6836.95	82+	0.88	81.54	93.93
Cmax (µg/dl)	2194.26	100	2476.06	100	0.89	85.04	92.35

+33 subjects in total (15 in test and 18 in RLD) are excluded from AUCi calculation due to nonlinear elimination phase or missing samples.

Per the product specific guidance (PSG) on Iron Sucrose Injection,[8,9] the applicant also conducted the in vitro particle size distribution (PSD) study by Dynamic Light Scattering. The PSD study is inadequate due to multiple deficiencies related to method validation.

- Based on an internal discussion on 01/04/2019,[10] it was determined that ferric oxyhydroxide is the active pharmaceutical ingredient (API) of both Velphoro® and Venofer®. The excipients of Venofer® were determined, at that time, to be sucrose, sodium hydroxide (used as pH adjuster), and water. Based on the new identification of API and excipient identification, the Q1/Q2 of the test product was re-evaluated in the BE addendum.[11] It is concluded that the formulation of the test and RLD products are still Q1/Q2 the same at that time.

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[7] Panorama, ANDA-212340-ORIG-1, Bioequivalence Review, Reviewer: Yun wang, 02/18/2020, A212340N000DB_N08282019.pdf; https://panorama.fda.gov/task/view?ID=5d67e9b9000718fa7680eb2c46e9558b

[8] Revised Nov 2013; https://www.accessdata.fda.gov/drugsatfda_docs/psg/Iron_sucrose_inj_21135_RV11-13.pdf

[9] Revised Sep 2021; https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_021135.pdf

(b)(4)

[11] Panorama, ANDA-212340-ORIG-1, Bioequivalence Review, Reviewer: Yun wang, 04/20/2020, A212340N000DB-Review01-Addendum08282019.pdf; https://panorama.fda.gov/task/view?ID=5d67e9b9000718fa7680eb2c46e9558b

- Per BE review of Amendment-9,[12] the applicant provided adequate responses to the deficiency related to bioanalytical batch acceptance criteria. The applicant adequately submitted the PSD method validation SOP and repeated PSD validation study with RLD product. Based on the assessor's population bioequivalence (PBE) statistical analysis, the volume-based D50, volume-based SPAN, and Polydispersity Index (PDI) of the test product all met BE acceptance criteria (95% upper confidence bound is ≤ 0 thus the particle size distribution of test product is deemed equivalent to that of the RLD product) as below:

In Vitro Population Bioequivalence Analysis- Assessor Calculation

D_{50} Summary

	Mean		Variability (%CV)							Mean Ratio (T/R)	
			Within Lot (n=10)					Between Lot (n=5)	Total (n=300)		
	Arith	Geo	Lot 1	Lot 2	Lot 3	Lot 4	Lot 5			Arith (n=300)	Geo (n=300)
Test	(b)(4)									0.95	0.95
Ref											

Span Summary

	Mean		Variability (%CV)							Mean Ratio (T/R)	
			Within Lot (n=10)					Between Lot (n=5)	Total (n=300)		
	Arith	Geo	Lot 1	Lot 2	Lot 3	Lot 4	Lot 5			Arith (n=300)	Geo (n=300)
Test	(b)(4)									1.00	1.00
Ref											

PDI Summary

	Mean		Variability (%CV)							Mean Ratio (T/R)	
			Within Lot (n=10)					Between Lot (n=5)	Total (n=300)		
	Arith	Geo	Lot 1	Lot 2	Lot 3	Lot 4	Lot 5			Arith (n=300)	Geo (n=300)
Test	(b)(4)									1.03	1.03
Ref											

From BE perspective, both fasting BE study (Study #RFR-P5-709) and in vitro PSD study (Study #IRSUS_REP DLS_IVC_V03) are **adequate**.

- The agency has identified -- as an excipient of the RLD as well.[13] In the BE addendum to ANDA 212340-Amendment-9, the agency considers NDA 021135 to contain the inactive ingredients, sucrose (Q.S. to 300 mg/mL), (b)(4)

[12] Panorama, ANDA-212340-ORIG-1-AMEND-9, Bioequivalence Review, Reviewer: Usha Katragadda, 08/12/2021, A212340N000DB-Review01-Amend12282020.pdf; https://panorama.fda.gov/task/view?ID=5fecbfda00de004de0a05eab1f8f1710

[13] R:\OGDS11\DIVISION\BIO\BIO1\Email Reference\208977 Iron Sucrose Injection\ Q1Q2 documentation for RLD table - start of draft .msg

(b)(4) [14,15] As per the Office of Pharmaceutical Quality (OPQ)'s drug product review for the current application (ANDA 212340),[16,17] (b)(4)

(b)(4)

(b)(4) Thus, the applicant's test formulation for ANDA 212340 is not Q1/Q2 the same as the RLD. The deficiency regarding Q1/Q2 sameness issue was informed to the applicant via the CRL issued on 04/17/2023.

4. SUBMISSION SUMMARY

Please refer to the BE review of the original submission for details. The drug product information, PK/PD information have not been revised since the original BE and amendment reviews completed on 02/18/2020 and 08/12/2021, respectively.

Per the current policy alert, there are two pending citizen petitions (CPs), #FDA-2005-P-0319 (2005P-0095) and #FDA-2021-P-0893.[18]

CP# FDA-2005-P-0319 (2005P-0095): This CP requests FDA to require identical manufacturing process, physico-chemical properties and BE standards. Currently no approval actions, no CRL, nor CC/IR/DRL for bioequivalence, filing labeling or quality prior to contacting policy lead. Note: The RLD's product formulation is being determined in light of the Velphoro CP response, which will impact any Q1/Q2 assessment, including for controls. OGDP will need to coordinate answering the CP with any approvals or tentative approvals, so please contact the Policy lead as soon as any application is possibly headed for an Approval Action (AP/TA).

CP# FDA-2021-P-0893: Petitioner request that the FDA reverse certain actions announced in its Citizen Petition Response dated May 26, 2021, FDA-2016-P-1163 (Response). In the Response, the Agency principally determined that the solid oral tablet Velphoro® (sucroferric oxyhydroxide) is not entitled to new chemical entity (NCE) exclusivity. Vifor offers no opinion on that issue. However, Vifor strongly disputes those portions of the Response that purport to change the established names and active ingredients of Velphoro and several IV iron products, including Venofer, to "ferric oxyhydroxide." Vifor also challenges the actions FDA has taken to implement

[14] GDRP: A208977 Drug Product-R04 AQ Final Date: 7/12/22
[15] R:\OGDS11\DIVISION\BIO\BIO1\Email Reference\208977 Iron Sucrose Injection\ RE Q1Q2 documentation for RLD table - start of draft (ANDA 208977).msg
[16] Panorama, ANDA-212340-ORIG-1-AMEND-9, Drug Product Quality Review, Reviewer: Dahui Liu, A212340 Drug Product R02b-IQ.docx; https://panorama.fda.gov/task/view?ID=5fecbfda00de02508b9c590a6ba7295f
[17] R:\OGDS11\DIVISION\BIO\BIO3\Email Communications\ANDA 212340 Iron Sucrose Injection\A212340_email communication with OPQ_NaCl in drug product.pdf
[18] Searched by "021135", Last accessed 03/25/2024; https://fda.sharepoint.com/sites/CDER-OGD-OGDP-OGDPAL/OGD%20Policy%20Alert%20List/Forms/Active%20Docs.aspx

that change in Drugs@FDA and the Orange Book. Currently no approval actions, no CRL, nor CC/IR/DRL for bioequivalence, filing labeling or quality prior to contacting policy lead. Note: The RLD's product formulation is being determined in light of the Velphoro CP response, which will impact any Q1/Q2 assessment, including for controls. OGDP will need to coordinate answering the CP with any approvals or tentative approvals, so please contact the Policy lead as soon as any application is possibly headed for an Approval Action (AP/TA).

5. REVIEW OF CURRENT AMENDMENT

Please refer to the BE addendum review dated 02/24/2023 for the assessment of Q1 and Q2 formulation sameness issue.[19] The Q1/Q2 sameness issue was discussed with Drug Product Quality (OPQ) reviewer and the deficiency language was concurred by the Office of Generic Drug Policy (OGDP) before communicated with the applicant. The applicant's response to the deficiency and the assessor's evaluation of the responses are provided in this section of the review.

5.1 Deficiency Related to the Test Formulation

DB Deficiency Comment #1:

Foley Hoag LLP submitted a Citizen Petition [Docket ID: FDA- 2016-P-1163] requesting, among other things, that FDA recognize that Velphoro (new drug application (NDA) 205109) is eligible for 5-year new chemical entity (NCE) exclusivity under 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the Federal, Food, Drug, and Cosmetic Act (FD&C Act) (Velphoro Citizen Petition). The Agency's response dated May 26, 2021 also states that "ferric oxyhydroxide is responsible for the pharmacological activity of both Velphoro and Venofer, and is thus the active ingredient in both drug products under the regulatory definition of "active ingredient" and additionally, "[s]ucrose and starches are merely excipients providing stability and processes functions…" (Reference: FDA Letter Response to Citizen Petition (CP), Docket No FDA-2016-P-1163, at 40 (May 26, 2021) (Velphoro Petition Response), available at: https://downloads.regulations.gov/FDA-2016-P-1163-0097/attachment_1.pdf).

Accordingly, we recommend you review the Agency's response and make any appropriate revisions to your application regarding active pharmaceutical ingredient (API) and inactive ingredients. Your proposed formulation provided in Module 3.2.P.1 is not qualitatively and quantitatively the same to the reference listed drug (RLD) with respect to one or more inactive ingredients.

FDA publishes new and revised product-specific guidances describing the Agency's current recommendations on demonstrating bioequivalence and certain other approval requirements. To ensure you are aware of FDA's recommendations for the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence (21 CFR 320.24(a)), please continue

[19] Panorama, ANDA-212340-ORIG-1-AMEND-9, Bioequivalence Review, A212340N000DB-Review01-Addendum12282020.pdf; https://panorama.fda.gov/task/view?ID=5fecbfda00de004de0a05eab1f8f1710

to monitor for the availability of new and revised product-specific guidances in the Federal Register and on the FDA Web site at the following address: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

Applicant's Response to Deficiency #1:

Sandoz acknowledges the FDA request and have updated Module 3.2.P.1 to properly identify the active ingredient, [redacted], with sucrose as now an excipient. Sandoz will continue to monitor the Agency's website for revisions to the product specific guidance and the Federal Register and FDA website for Citizen Petition updates.

Assessor's Comments on Applicant's Response to Deficiency #1:

- The applicant revised the nomenclature of API from iron sucrose to ferric oxyhydroxide and added sucrose as an inactive ingredient. The composition table for the test product is revised as follows:

Original composition table of the drug product [20]

Unit Dose Composition of Iron Sucrose Injection, 100mg/5mL:

Ingredient	Function	Amount per mL	Amount per vial	% w/v	IIG[1] Limit (Injection)
Iron Sucrose	Active Pharmaceutical Ingredient	20 mg elemental iron	(b)(4)		
Sodium Hydroxide, NF	pH Adjustment	q.s. to pH 10.5 – 11.1			
Water for Injection, USP	Solvent	[redacted]			
[redacted]					

(b)(4)

Revised composition table of the drug product [21]

Unit Dose Composition of Ferric Oxyhydroxide Injection, 100mg/5mL:

(b)(4)

(b)(4)

[20] DocuBridge, ANDA 212340, #0001(1) 08/28/2019, Module 3.2.P.1 Description and Composition of the Drug Product; \\CDSESUB1\EVSPROD\anda212340\0001\m3\32-body-data\32p-drug-prod\iron-sucrose-injection-rafarm-sa\32p1-desc-comp\fp-description-and-composition.pdf

[21] DocuBridge, ANDA 212340, #0013(13) 08/18/2023, Module 3.2.P.1 Description and Composition of the Drug Product; \\CDSESUB1\EVSPROD\anda212340\0013\m3\32-body-data\32p-drug-prod\iron-sucrose-injection-rafarm-sa\32p1-desc-comp\fp-description-and-composition.pdf

The assessor verified that the applicant made changes in Section 3.2.P.5.1 (Control of Drug Product-Specifications) and Section 3.2.P.5.2 (Control of Drug Product-Analytical Procedures). However, the applicant did not change the Chemical Product Name in Form FDA 356h.

The formulation of other two strengths of the test product, Iron Sucrose Injections, EQ 50 mg Iron/2.5 mL and EQ 200 mg Iron/10 mL is proportional similar to the formulation of the bio-strength (EQ 100 mg base/5 mL), which underwent acceptable in vivo and in vitro testing.

- As stated in the addendum BE review dated 02/24/2023,[22] in the case of current ANDA 212340, DMF (b)(4) was used. (b)(4) as per the DMF # (b)(4).[23] However, the applicant is not aware of the Q1/Q2 issue due to the disclosure of DMF information. (b)(4) (b)(4)

- The most recent consideration on the composition of the RLD formulation table is shown below, as suggested in the OPQ review:[25]

RLD Formulation (Not to be released under FOIA)

(b)(4)

Qualitative and Quantitative Comparison between Test and RLD formulations (Not to be released under FOIA)

(b)(4)

[22] Panorama, ANDA-212340-ORIG-1-AMEND-9, Bioequivalence Review, A212340N000DB-Review01-Addendum12282020.pdf; https://panorama.fda.gov/task/view?ID=5fecbfda00de004de0a05eab1f8f1710

(b)(4)

[25] Panorama, ANDA-212340-ORIG-1-AMEND-13, Drug Product Quality Review; https://panorama.fda.gov/task/view?ID=64e5746f00586d4edd75f1907c2453fc

(b)(4)

Although (b)(4) has not been listed in the test formulation composition table, after the internal discussion with OPQ, OPQ updated the review,[26] (b)(4) (b)(4) (b)(4) Therefore, the test drug product is deemed Q1/Q2 based on our internal information.

- Based on the above information, our internal Q1/Q2 evaluation indicates that the test product formulation is acceptable. Per previous BE assessments,[27,28] the in vivo fasting BE study (Study #RFR-P5-709) and in vitro PSD study (Study #IRSUS_REP DLS_IVC_V03) were deemed acceptable. The formulation of other two strengths of the test product, Iron Sucrose Injections, EQ 50 mg Iron/2.5 mL and EQ 200 mg Iron/10 mL is proportional similar to the formulation of the bio-strength (EQ 100 mg base/5 mL), which was used for in vivo and in vitro BE studies. The waiver requests of in vivo and in vitro BE studies for the test product, Iron Sucrose Injections, EQ 50 mg Iron/2.5 mL and EQ 200 mg Iron/10 mL, are granted.

- As a result, there are no BE deficiencies in the current BE assessment. Based on the internal discussion with OGDP, no BE deficiency for this ANDA will be issued at this stage.

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[26] Panorama, ANDA-212340-ORIG-1-AMEND-13, Drug Product Quality Review; https://panorama.fda.gov/task/view?ID=64e5746f00586d4edd75f1907c2453fc

[27] Panorama, ANDA-212340-ORIGI-1, Bioequivalence Review, Reviewer: Yun Wang (4); https://panorama.fda.gov/task/view?ID=5d67e9b9000718fa7680eb2c46e9558b

[28] Panorama, ANDA-212340-ORIG-1-AMEND-9, Bioequivalence Review, Reviewer: Usha Katragadda; https://panorama.fda.gov/task/view?ID=5fecbfda00de004de0a05eab1f8f1710

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	212340
APPLICANT:	Sandoz Inc.
DRUG PRODUCT:	Iron Sucrose Injection, EQ 20 mg Iron/mL (EQ 50 mg Iron/2.5 mL, EQ 100 mg Iron/5 mL, and EQ 200 mg Iron/10 mL)

The Division of Bioequivalence III (DBIII) has completed its review of your submission acknowledged on the cover sheet and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns are raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

April C. Braddy, Ph.D., RAC
Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

6. OUTCOME PAGE

Completed Assignment for 212340 ID: 53374

Reviewer:	Myung, Ja Hye	**Date Completed:**	
Verifier:	,	**Date Verified:**	
Division:	Division of Bioequivalence		
Description:	A212340-Amendment 13-Iron Sucrose Injection, EQ 20 mg Iron/mL (Sandoz)		

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*		
53374	8/18/2023	Parallel2024	Other (Minor amendment - original or supplement) [1]	1	1	Edit	Delete

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	212340	
Drug Product Name	Iron Sucrose Injection, USP*	
Strength(s)	Eq. 20 mg base/mL (50 mg/2.5 mL, 100 mg/5 mL, 200 mg/10 mL)	
Applicant Name	Sandoz Inc.	
Applicant Address	100 College Road West Princeton, NJ 08540	
US Contact Name	Gregory Seitz, Director Regulatory Affairs	
US Contact Telephone Number	(b)(6)	
US Contact Fax Number	(973) 781-3710	
Original Submission Date(s)	8/29/2019 (Original Submission)	
Submission Date(s) of Amendment(s) Under Review	04/16/2020 (supporting document #6) – DRL response (currently reviewed) 12/28/2020 (supporting document #9) – CRL response (currently reviewed) Assessor notes: Bioequivalence CRL response dated 12/28/2020 refers to the applicant Bioequivalence DRL response dated 04/16/2020	
Primary Reviewer	Usha Katragadda, Ph.D.	
Secondary Reviewer	Moheb Makary, Ph.D.	
Tertiary Reviewer	Ke Ren, Ph.D.	
Study Number(s)	RFR-P5-709	IRSUS_REP DLS_IVC_V03
Study Type(s)	Fasting (Pivotal)	In vitro BE (Particle size distribution)
Strength(s)	1 x 100 mg/5 mL	1 x 100 mg/5 mL
Clinical Site	Algorithme Pharma Inc.	N/A
Clinical Site Address	1200 Beaumont Ave. Mount-Royal, Quebec, Canada H3P 3P1	N/A
Analytical Site		
Analytical Site Address	(b)(4)	

	H7V 4B3		
OSIS status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☐ **Complete** ☐ **N/A (Waiver/Deem Bioequivalent)**	**Post October 1, 2014 ANDAs** ☒ **Complete** ☐ **Pending For Cause Inspection** ☐ **Pending** ☐ **N/A**	
Waiver	☒ **Granted** ☐ **Tentatively granted** ☐ **Not granted** ☐ **N/A**		
QC Dissolution	☐ **Pending** ☐ **Adequate** ☐ **Inadequate** ☒ **N/A**		
Formulation	☒ **Adequate** ☐ **Inadequate**		
Will Response to CR Result in a Reformulation?	☐ **Possibly** ☐ **No** ☒ **N/A**		
Deficiency Classification	☐ **Major** ☐ **Minor/IR** ☒ **N/A (review is adequate)**		
Major Deficiency Theme	N/A		
Justification for Major Designation	N/A		
Overall Review Result	☒ **Adequate** ☐ **Inadequate**		
Product Specific Guidance (PSG) Referenced in Review	☒ **Recommended/Latest Revision Date: Nov, 2013** **RLD/RS Number: 021135**[1] **Assessor' note:** There is an ongoing PSG revision project for this product (https://panorama.fda.gov/project/view?ID=548ae648002138292f02215b409bf1b6). BE assessment was conducted in accordance with posted PSG in addition to ongoing discussion within ORS about future PSG revisions (e.g. PSD assessed based on Z-average and PDI or D50 (v) and Span (v)). The proposed updated version to PSG does not impact the current ANDA. ☐ **N/A (no PSG available at time of review)**		
Revised/New Draft Guidance Generated as Part of Current Review	☐ **YES** ☒ **NO**		
Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**
1, 6, 9	**Fasting**	100 mg/5 mL	☒ **Adequate** ☐ **Inadequate**
1, 6, 9	**In vitro (Particle Size Distribution)**	100 mg/5 mL	☒ **Adequate** ☐ **Inadequate**

[1] https://www.accessdata.fda.gov/drugsatfda_docs/psg/Iron_sucrose_inj_21135_RV11-13.pdf

1, 6, 9	**Waivers**	50 mg/2.5 mL and 200 mg/10 mL	☒ **Adequate** ☐ **Inadequate**

* There are several different reference drugs that use the active ingredient, ferric oxyhydroxide (e.g. Venofer, Ferrlecit, INFED, and [redacted] The current ANDA under review is referencing Venofer, previously identified as Iron Sucrose.

1 EXECUTIVE SUMMARY

This is an assessment of Complete Response Letter (CRL) response amendment (major) submitted on 12/28/2020[2].

In the original submission dated August 29, 2019, [3] Sandoz Inc.'s submitted the results of a fasting BE study comparing a test product, Iron Sucrose Injection USP, EQ 100 mg base/5 mL (EQ 20 mg base/mL), to the corresponding reference product, American Regent Inc's, Venofer® (iron sucrose) Injection USP, EQ 100 mg base/5 mL (EQ 20 mg base/mL) NDA 021135, approved on November 6, 2000. The pivotal in vivo BE study (#RFR-P5-709) and pivotal in vitro particle size distribution (PSD) study (#IRSUS_REP DLS_IVC_V03[redacted]) were found inadequate due to bioanalytical batch acceptance criteria and insufficient PSD method validation deficiencies.[4] CR letter was sent to the applicant with BE deficiencies dated on June 26, 2020.

In the current amendment, the applicant provided adequate responses to the deficiencies listed in CR letter. Deficiency related to bioanalytical batch acceptance criteria is adequate as the bioanalytical plan include the coefficient of determination (R2) should be $\geqslant$ 0.9800. The applicant adequately submitted the PSD method validation SOP and repeated PSD validation study with reference product and submitted PSD validation study results are acceptable. The applicant confirmed that five test product batches in PSD study were manufactured using same manufacturing process as well as the same API lots. In the current submission, the applicant provided in vitro testing data of every individual measurements of PSD study (D10, D50, D90 and Span for intensity, volume and number; and Polydispersity Index). The results for pivotal in-vitro study is summarized below:

[2] DocuBridge: ANDA 212340, Sequence 0009, Submission date: 12/28/2020.
[3] DocuBridge: ANDA 212340, Sequence 0001, Submission date: 08/29/2019.
[4] GDRP, ANDA-212340-ORIG-1, Bioequivalence Review, A212340N000DB-Review01-Addendum08282019 - Archived PDF Yun wang, 04/20/2020
https://panorama.fda.gov/task/view?ID=5d67e9b9000718fa7680eb2c46e9558b

In Vitro Particle Size Distribution (PSD) Study # IRSUS_PRT_DLS_IVC_V03

Consistent with the current Product Specific Guidance (PSG) on Iron Sucrose Injection, the applicant submitted a pivotal in vitro PSD BE study # IRSUS_PRT_DLS_IVC_V03 in the original submission.

The applicant conducted the study on five test and reference lots. For each lot, the study was conducted on 10 vials with three preparations per vial and two measurements per preparation. Based on assessor's population bioequivalence (PBE) statistical analysis, the volume-based D50, volume-based SPAN, and Polydispersity Index (PDI) of the test product all met BE acceptance criteria (95% upper confidence bound is ≤ 0 thus the particle size distribution of test product is deemed equivalent to that of the reference product). This data in current submission is considered acceptable per the product specific guidance for Iron Sucrose Injection[5].

In Vitro Population Bioequivalence Analysis- Assessor Calculation

D_{50} Summary											
	Mean		Variability (%CV)							Mean Ratio (T/R)	
			Within Lot (n=10)					Between Lot (n=5)	Total (n=300)		
	Arith	Geo	Lot 1	Lot 2	Lot 3	Lot 4	Lot 5			Arith (n=300)	Geo (n=300)
Test	(b)(4)									0.95	0.95
Ref											

Span Summary											
	Mean		Variability (%CV)							Mean Ratio (T/R)	
			Within Lot (n=10)					Between Lot (n=5)	Total (n=300)		
	Arith	Geo	Lot 1	Lot 2	Lot 3	Lot 4	Lot 5			Arith (n=300)	Geo (n=300)
Test	(b)(4)									1.00	1.00
Ref											

PDI Summary											
	Mean		Variability (%CV)							Mean Ratio (T/R)	
			Within Lot (n=10)					Between Lot (n=5)	Total (n=300)		
	Arith	Geo	Lot 1	Lot 2	Lot 3	Lot 4	Lot 5			Arith (n=300)	Geo (n=300)
Test	(b)(4)									1.03	1.03
Ref											

In the current amendment, the applicant provided adequate responses to the deficiency comments related to bioanalytical batch acceptance criteria, the pre-study method validation, and the PSD study # IRSUS_PRT_DLS_IVC_V03 .

[5] GDRP, Ferric Oxyhydroxide Intravenous Injectable NDA 021135 Revision PSG, Ferric oxyhydroxide intravenous injectable NDA 021135 Review RV - Not Archive, 05/27/2021 https://panorama.fda.gov/task/view?ID=5c7d8e6900142a80731733eed3152a33

The formulation of the EQ 50 mg base/2.5 mL and EQ 200 mg base/10 mL strengths of the test product is proportionally the same as that of the bio-strength (EQ 100 mg base/5 mL). All strengths of the test product are considered qualitatively (Q1) and quantitatively (Q2) the same to the corresponding strength of the RLD products. Based on the information provided, the DB grants the waiver of in vivo BE study requirements for Iron Sucrose Injection, EQ 50 mg base/2.5 mL and EQ 200 mg base/10 mL.

OSIS status for Clinical and Analytical sites for in Vivo PK Study
Per the original BE review, the OSIS status for the clinical and analytical sites (Algorithme Pharma Inc.) is complete.[6,7] In addition, the studies submitted in the current ANDA do not indicate any conduct issues and no data integrity deficiencies were identified by the assessor. The OSIS inspection status of the current ANDA is **complete.**

OSIS status for In Vitro BE site
Per the EIR, the inspection at In Vitro BE site [Rafarm S.A.] is classified as No Action Indicated (NAI)[8]. In addition, the study submitted in the current ANDA does not indicate any conduct issues and no data integrity deficiencies were identified by the assessor. The OSIS inspection status of the current ANDA is **complete**.

The application is **adequate** from BE perspective.

NOTE:
As of 06/18/2021, there are two policy alerts from OGDP related to Iron Sucrose Injection (Docket #FDA-2020-P-0158 and #FDA-2005-P-0319 (2005P-0095), please see Review Section 3 **Background** for details.

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[6] GDRP, ANDA 212340-Orig-1, Clinical PK/PD Sites, Site: Algorithme Pharma Inc, Document name: Decline to Inspect_NAI Memo_212340_Alta Sciences_Clinical.pdf, 10/1/2019
[7] GDRP, ANDA 212340-Orig-1, Analytical Sites, Site: Algorithme Pharma Inc, Document name: EIR Cover Memo Altasciences Laval Canada.pdf, 11/20/2019.
[8] GDRP, ANDA 212340, In Vitro BE Sites, Rafarm S.A., Completed 05/29/2020.
https://panorama.fda.gov/task/view?ID=5daf137100a00795af25f29d7559cf02

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3 Background

- The original application contains the results of a fasting bioequivalence (BE) study comparing a test product, Sandoz Inc.'s Iron Sucrose Injection, Eq. 20 mg base/mL, to the corresponding reference product, American Regent Inc's Venofer® (iron sucrose) Injection, EQ 100 mg Iron/5 mL (EQ 20 mg Iron/mL). The BE study was designed as a single-dose, two-treatment, fourteen-group, parallel study in healthy male and female subjects. The *in vivo* fasting BE study results are summarized in the table below.

Iron Sucrose USP Injection (No of subjects completed = 200) Dose: 1 x 100 mg Least Squares Geometric Means*, Ratio of Means (%), and 90% Confidence Intervals (%)							
Pivotal Fasted Bioequivalence Study (Study No.RFR-P5-709)							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *µg/dl)	5548.15	100	6367.12	100	0.87	81.92	92.68
AUC∞ (hr *µg/dl)	5983.54	85*+	6836.95	82*+	0.88	81.54	93.93
Cmax (µg/dl)	2194.26	100	2476.06	100	0.89	85.04	92.35

+The following subjects are excluded from AUCi calculation due to nonlinear elimination phase or missing samples. **TI**: Test: Subject Nos. (b)(6)

TBI: Test: Subject Nos. (b)(6) Ref: Subject Nos. (b)(6)

(b)(6)

The final subject exclusion will be: **Test (15)**: (b)(6)

- **Ref (18)**: Subject Nos. (b)(6)

- The 90% CIs for the test/reference ratios of least square geometric means of LnC_{max}, $LnAUC_{0-t}$ and $LnAUC_{\infty}$ of iron sucrose-associated iron fall within the acceptance range of 80.00-125.00% in the fasting BE study (Study No. RFR-P5-709). Per the original BE review[9], the applicant's fasting study is inadequate due to bioanalytical deficiency.

- Based on internal Agency discussion on Friday January 4, 2019, it was determined that in order to maintain consistency with the handling of Velphoro ANDA reviews, that ferric oxyhydroxide is considered to be the active pharmaceutical ingredient (API) of Iron Sucrose[10]. Therefore, the excipients of Venofer® (iron sucrose) Injection are sucrose, sodium hydroxide (used as pH adjuster), and water. As of 07/22/2021 chemical composition (CC) tables of test and RLD formulation and RLD label, active ingredient is iron sucrose. Given the conclusion of the Velphoro CP (FDA-2016-P-1163 by Vifor Fresenius), ferric oxhydroxide is responsible for the pharmacological

[9] GDRP, ANDA-212340-ORIG-1, Bioequivalence Review, Yun wang, 02/18/2020
https://panorama.fda.gov/task/view?ID=5d67e9b9000718fa7680eb2c46e9558b

(b)(4)

activity of both Velphoro and Venofer, and is thus the active ingredient in both drug products under the regulatory definition of "active ingredient" and additionally, (b)(4) (b)(4) The composition table is needed to update. There is ongoing discussion on how to provide specific directions to ANDA applicants and NDA sponsor and RLD labelling changes regarding ferric oxyhydroxide is the API instead of Iron sucrose.

- Per original BE review[11] and BE addendum,[12] the formulation of the test and reference products are Q1/Q2 the same. As of 07/22/2021, the Q1/Q2 evaluation is based on (b)(4) (b)(4) (b)(4) The test formulation is acceptable. The formulations for 50 mg/2.5 mL and 200 mg/10 mL strengths are proportionally similar to the bio-strength 100 mg/5 mL which underwent BE testing.

Formulation Comparison between Test and RLD

Ingredient name and standard	ANDA's formula	RLD Venofer® (Iron Sucrose Injection, USP)	Function in Formulation	Difference between T and R in %
(b)(4)				

[11] GDRP, ANDA-212340-ORIG-1, Bioequivalence Review, Yun wang, 02/18/2020 https://panorama.fda.gov/task/view?ID=5d67e9b9000718fa7680eb2c46e9558b

[12] GDRP, ANDA-212340-ORIG-1, Bioequivalence Review, A212340N000DB-Review01-Addendum08282019 - Archived PDF Yun wang, 04/20/2020 https://panorama.fda.gov/task/view?ID=5d67e9b9000718fa7680eb2c46e9558b

[13] GDRP, ANDA-212340-ORIG-1, Bioequivalence Review, A212340N000DB-Review01-Addendum08282019 - Archived PDF Yun wang, 04/20/2020 https://panorama.fda.gov/task/view?ID=5d67e9b9000718fa7680eb2c46e9558b

(b)(4)

(b)(4)

- Per draft product specific BE guidance for iron sucrose Injection, the applicant also conducted the *in vitro* particle size distribution test by Dynamic Light Scattering. The particle size distribution testing was **inadequate** due to the multiple deficiencies related to method validation.

- In current submission the applicant sent response to bioanalytical deficiency and deficiencies related to *in vitro* particle size distribution test.

CP #FDA-2020-P-0158

This CP requests FDA to:

- Issue guidance, and publicly affirm, that the ANDA approval pathway is not appropriate for harder-to-copy complex drugs already identified by FDA; that FDA's planned guidance on therapeutic equivalence for follow-on drugs approved pursuant to Section 505(b)(2) make clear that a follow-on harder-to-copy complex drug may be determined to be therapeutically equivalent to its reference listed drug, when the two drugs meet the existing criteria, namely, they have: (1) the same active ingredient; (2) the same route of administration, dosage form, and strength; (3) the same clinical effect and safety profile; and (4) been shown to be bioequivalent.

No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL for Filing or Quality.

CP #FDA-2005-P-0319

This CP requests FDA to require identical manufacturing process, physico-chemical properties, BE standards. No Approval Actions (TA/AP) can be taken prior to contacting Policy Lead. No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL for Bioequivalence or Quality. As of June 2021, the affected ANDA's are: 212340, (b)(4) (b)(4), 212559, and (b)(4) OGDP will need to coordinate answering the CP with any approvals or tentative approvals, so please contact the Policy lead as soon as any application is possibly headed for an Approval Action (AP/TA). It is suggested to contact Policy prior to issuing either a CRL, or a DRL for Bioequivalence or Quality.

4 Review of Current Amendment

Deficiency Related to Pivotal Fasting Bioequivalence Study (#RFR-P5-709)

4.1 FDA Deficiency #1

You rejected analytical batches for both (b)(4) assays based on "The coefficient of determination was (b)(4)". However, this criterion was not documented in your standard operation procedure (SOP) No. (b)(4). Please provide evidence to support why you pre-set (b)(4) as R2 cutoff.

Applicant Response#1:

Based on the review of the method performance data the coefficient of determination of R2 (b)(4) was applied as one of the conditions for run acceptance. Similar criteria has been used in several bioanalytical method SOPs (i.e. LAS SOPs) for (b)(4) (b)(4) (b)(4) This criteria for batch acceptance was used for both method validation and sample analysis work and was established prior to the start of pharmacokinetic sample analysis work.

The acceptance criteria for calibration curve has been revised to be suitable to this type of assay. Refer to the Supplementary Information (SI) "Revised Acceptance Criteria for Validation A" and "Revised Acceptance Criteria for calibration Curve A". These SIs are on file at Altasciences.

As per (b)(4) SOP (b)(4) "The same procedures for acceptance criteria and reporting of results should be used throughout the study. In the case where the study protocol conflicts with general SOPs (e.g. LAP SOPs) and/or bioanalytical method SOPs (LAS SOPs), the protocol takes hierarchical precedence followed by the Bioanalytical Study Plan over general SOPs…". The R^2 acceptance criterion is method specific as documented in the bioanalytical plan for both assays. Both bioanalytical plans for both assays (attachments 1 and 2) were finalized and signed prior to the start of sample analysis in accordance to our established procedures, as detailed in SOP (b)(4) (b)(4) Both bioanalytical plans are available in Appendix 2 of each bioanalytical report and the referenced SOP is available in Appendix 5. The detailed method SOPs (specific for each assay) are on file at Altasciences.

The coefficient of determination determines how well the regression model fits the observed data and how variation in the covariate (x) can determine the variation in the outcome (y). For example, (b)(4)

(b)(4)

(b)(4) Therefore, in addition to precision and accuracy acceptance criteria on the calibration curve, it is necessary to add the R^2 acceptance criterion in order to have a stringent rule on a linear regression model.

Attachment 1: rfr-p5-709-bio-plan-tas.pdf (section 2.6)
Attachment 2: rfr-p5-709-bio-plan-tts.pdf (section 2.6)

Assessor's Assessment to Applicant's Response #1:

- The applicant was asked to provide the evidence to support why the applicant pre-set [redacted] as R^2 cutoff for batch acceptance criteria as this criteria cannot be found in the standard operation procedure (SOP) No. [redacted]. The applicant reported that the coefficient of determination of R2 [redacted] was applied as one of the conditions for run acceptance in several bioanalytical method SOPs [redacted]

(b)(4)

- The criteria R2 [redacted] for batch acceptance was used for both method validation and sample analysis work and was established prior to the start of pharmacokinetic sample analysis work. The assessor verified the method validation report[16] of [redacted] and found that in revision 2 method validation of [redacted] run# [redacted] is rejected due to R2 [redacted] and this run [redacted] is conducted prior to the sample analysis runs which were rejected for the same reason (starting at [redacted] for [redacted] and [redacted] for [redacted]

[16] \\CDSESUB1\evsprod\anda212340\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\rfr-p5-709-an\ap-3-valid-rpt-tts.pdf (Page#30)

Table 1. Summary of Evaluation Acceptance or Rejection

Batch Identification	Sample Preparation Date/ Batch Date	Preparation Date of Calibrants and QC Samples	Evaluation	Total Serum Iron Status / Comments / System ID
(b)(6)			Test Curve: Analyst Competency	Rejected (b)(4)

- Per SOP (b)(4) (Sample (b)(4), effective (b)(4)

The same procedures for acceptance criteria and reporting of results should be used throughout the study. In the case where the study protocol conflicts with general SOPs (e.g. LAP SOPs) and/or bioanalytical method SOPs (LAS SOPs), the protocol takes precedence followed by the Bioanalytical Plan over SOPs. All required validation assessments should be

Therefore, assessor agrees that bioanalytical plan takes precedence over SOPs.

- Per bioanalytical plan of TSI[17] and TSB[18] standard curve acceptance criteria include that the coefficient of determination (R2) should be (b)(4) and both bioanalytical plans are dated (b)(6) prior to bioanalytical analysis dates (b)(6)

- The applicant reported that the validation of (b)(4) (b)(4), 51 out of 52 runs had an R2 (b)(4), which represents -- % of the data. Therefore, in addition to precision and accuracy acceptance criteria on the calibration curve, it is necessary to add the R2 acceptance criterion in order to have a stringent rule on a linear regression model.

- As the justifications stated above. assessor agrees with R2 (b)(4) as batch acceptance criteria.

The applicant's response to deficiency#1 is adequate.

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[17] \\CDSESUB1\evsprod\anda212340\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\rfr-p5-709-an\ap-2-bio-plan-tts.pdf (page# 12/14)

[18] \\CDSESUB1\evsprod\anda212340\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\rfr-p5-709-an\ap-2-bio-plam-tas.pdf

Deficiencies Related to Particle Size Distribution (PSD) Study (Deficiencies # 1 -4)

4.2 FDA Deficiency #1

Please submit SOP for method validation of PSD study by dynamic light scattering. Please also provide study date for your PSD study.

Applicant Response #1:

As per the Agency's request, the in-house SOP for method validation of PSD study by dynamic light scattering [redacted] Version III is provided in Module 3.2.P.5.3. Sandoz would like to clarify that validation of the analytical method for the PSD study was performed according to the previous version number II of SOP [redacted] and the changes between previous and current version of the SOP's does not impact the [redacted] method validation section of the SOP. The details between version II and version III are listed in the history of changes on the pages 41 and 42.

As per this SOP, analytical procedures are categorized in four types:

I. Analytical methods for the quantitation of the major components of drug substances and drug products.
II. Analytical methods for the determination of impurities in drug substances or degradation products in drug products. These methods include a) quantitative assays and b) limit tests.
III. Analytical methods for the determination of performance characteristics (e.g. dissolution and drug release) for the product. In this category could fit qualitative physical property measurements such as particle size.
IV. Identification tests.

Furthermore, it is mentioned in the SOP, that qualitative physical property measurements, such as particle size, which could impact performance characteristics, often best fit in Category III. The proposed methodology for Category III includes the evaluation of the following elements:

1. Linearity
2. Accuracy
3. Precision
4. Range
5. Specificity
6. Robustness
7. Stability of Solution

In the relevant validation study, covered by the protocol no [redacted] Precision [redacted] and Robustness were evaluated. Furthermore, during the method development, a concentration range of [redacted] to [redacted] was established for which the measured particle size distribution was not affected by changes in concentration. The following elements were excluded based on

the rationale recorded in the protocol: Linearity, Specificity and Accuracy, while the Stability of solution study was not part of the validation since all measurements are performed with fresh solutions.

PSD study measurement dates

The dates of the PSD study ((b)(4) and relevant report (b)(4) and (b)(4) are presented in the following table:

Sample Batch Number	Comments /Sample Details	Analysis Date (Vials tested)
(b)(4) (b)(6)		

Sample Batch Number	Comments /Sample Details	Analysis Date (Vials tested)
(b)(4) (b)(6)		

Assessor's Assessment to Applicant's Response #1:

- The applicant submitted requested SOP for method validation of PSD study by dynamic light scattering SOP (b)(4) effective date: (b)(4)
- Assessor verified that per SOP (b)(4) particle size analytical procedure is part of the Category III analytical procedures mentioned in the SOP.
- In the relevant validation study, covered by the protocol no (b)(4), & report no (b)(4)

(b)(4) and Robustness were evaluated. Furthermore, during the method development, a concentration range of (b)(4) to (b)(4) was established for which the measured particle size distribution was not affected by changes in concentration. The applicant mentioned parameters above are acceptable for the particle size validation study.

- The applicant provided the PSD study dates (refer to table above in the applicants response). The manufacture month of two lots were not given in the table for lot# IRSUS/22 and IRSUS/25. Per pharmaceutical development report[19] Mnf date of lot# IRSUS/22 and IRSUS/25 is 12/2017. The assessor confirmed at the time the PSD study# IRSUS_PRT_DLS_IVC_V03 was conducted, all investigational drug products were not expired. (i.e. test product was used within 2 year stability window[20]).

The assessor deems the applicant's response to deficiency #1 is acceptable.

4.3 FDA Deficiency #2

You used five test product batches (two demo batches: #IRSUS/22, IRSUS/25; three exhibit batches: 801859, 801863, and 801869) in PSD study. Please clarify if there is any difference among all five test product batches,) in terms of manufacturing process, in-process controls and specifications.

Applicant Response #2:

Sandoz would like to clarify that during the Pre-ANDA Product Development meeting, Sandoz proposed to the Agency if 5 lots can be used for the PSD Study (2 demonstration batches, which were manufactured 6 months prior to the manufacture of 3 exhibit batches and the 3 exhibit batches). During the discussion in the Pre-ANDA Product Development meeting, the FDA agreed that this approach is acceptable. Additionally, Sandoz would like to inform the Agency that the manufacturing process as well as the same API lots were utilized in all 5 batches.

Assessor's Assessment to Applicant's Response #2:

The applicant confirmed that the five test product batches (two demo batches: #IRSUS/22, IRSUS/25; three exhibit batches: 801859, 801863, and 801869) in PSD study were manufactured using same manufacturing process as well as the same API lots.

The applicant's response to deficiency #2 is acceptable.

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[19] \\CDSESUB1\evsprod\anda212340\0001\m3\32-body-data\32p-drug-prod\iron-sucrose-injection-rafarm-sa\32p2-pharm-dev\pharmaceutical-development.pdf

[20] \\CDSESUB1\evsprod\anda212340\0009\m3\32-body-data\32p-drug-prod\iron-sucrose-injection-rafarm-sa\32p8-stab\stability-data.pdf

4.4 FDA Deficiency #3

You used test product (lot #IRSUS/25, 2017 demo batch) to conduct pre-study method validation for precision (Study report No. IRSUS_AMV_REP_DP_DLS_V01). Since the test product is not an approved drug product at the time of submission, it is not appropriate to be used in method validations. Please repeat pre-study method validation for precision, intermediate precision, repeatability and ruggedness using the reference product.

Applicant Response #3:

As per the Agency's request, the analytical method validation for the PSD study have been repeated was repeated using the Reference Product (Venofer). The method validation report (IRSUS_AMV_REP_DP_DLS_V02) and the typical histograms are provided in Module 3.2.P.5.3.

Assessor's Assessment to Applicant's Response #3:

- The applicant repeated and reported[21] pre-PSD study method validation using the Reference Product (Venofer).
- Assessor checked and confirm that the same procedure was used to prepare sample for study sample analysis and method validation.

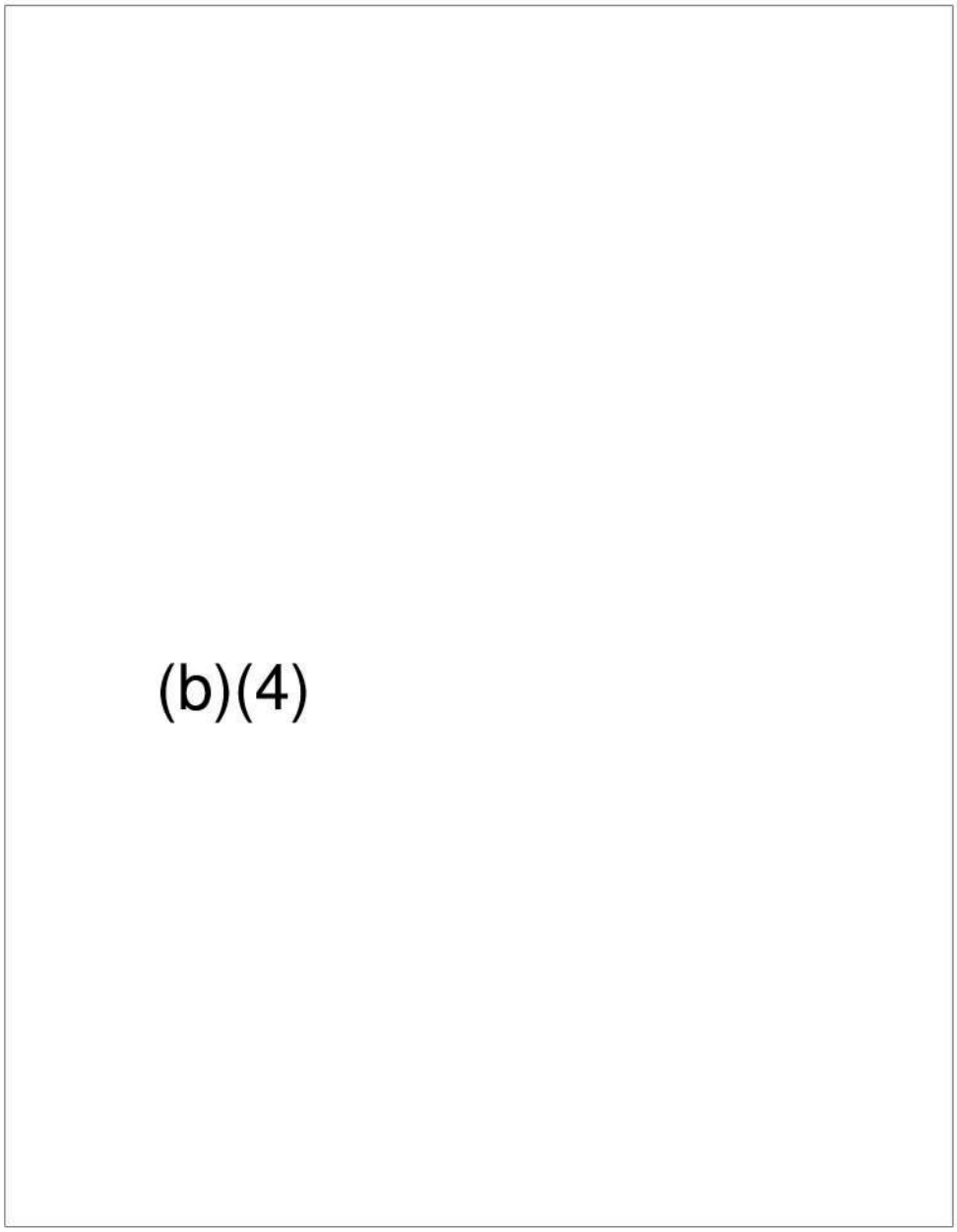
(b)(4)

- The applicant validated the assay precision (intermediate precision and repeatability) and robustness of the method. The validation results meet acceptance criteria. Based on the applicant's measurement, D_{10}, D_{50} and D_{90} for the reference product are listed as below.

[21] \\CDSESUB1\evsprod\anda212340\0006\m3\32-body-data\32p-drug-prod\iron-sucrose-injection-rafarm-sa\32p5-contr-drug-prod\32p53-val-analyt-proc\analyt-meth-val-size-distr.pdf

(b)(4)

(b)(4)



- As a result, the applicant's method validation for PSD testing is **adequate** per above comments.

The applicant's response to deficiency #3 is adequate.

4.5 FDA Deficiency #4

For PSD study by dynamic light scattering, you stated that you performed two measurements per preparation and reported the results as arithmetic average of two measurements for each preparation. Please provide in vitro testing data with every individual measurement in SAS transport file (.xpt) using the following format.

PRODUCT	LOT	VIAL/Measurement		D10	D50	D90	SPAN	Polydispersity Index
TEST	1234	1	Measurement 1					
			Measurement 2					
		1	Measurement 1					
			Measurement 2					
		1	Measurement 1					
			Measurement 2					
		2	Measurement 1					
			Measurement 2					
		2	Measurement 1					
			Measurement 2					
		2	Measurement 1					
			Measurement 2					
		n	Measurement 1					
			Measurement 2					

Applicant Response #4:

As per the Agency's request, the in vitro testing data of all individual measurements acquired is provided below in the SAS transport file (.xpt) format.
define-pdi-psd.pdf
pdi-psd.xpt
pdi-psd.pdf

Assessor's Assessment to Applicant's Response #4:

- PSD study# IRSUS_PRT_DLS_IVC_V03 was conducted to compare the particle size distribution of the (b)(4) l presentation ((b)(4)) (IRSUS/22, IRSUS/25, 801859, 801863 and 801869) to the RLD (b)(4) presentation (20 mg/mL) (7284,7258, 7319A, 7353 and 7279). The applicant provided the results for the study in the original application but did not provide SAS transport file or the in vitro testing data of individual measurements of PSD study. The applicant was asked to provide this information.

- In the current submission, the applicant provided in vitro testing data of individual measurements of PSD study (D10, D50, D90 and Span for intensity, volume and number; and Polydispersity Index) for each of the 10 vials tested for each of the five batches from test product and Venofer®. Ten separate vials of each drug product were used and three preparations per vial were made and two measurements per preparation were performed. The assessor confirmed that the test and reference were not expired at the time of study initiation.

- As requested the applicant provided PSD individual measurements data for D10, D50, D90, Span and PDI. The assessor performed independent statistical analysis and per assessor's analysis, the upper bound of 95% CI for D50, SPAN and PDI met the PBE acceptance criteria. This data in current submission is considered

acceptable per the product specific guidance for Iron Sucrose Injection [22] (Bioequivalence based on (95% upper confidence bound): Z-average and PDI or D50 and SPAN using the population bioequivalence statistical approach). The following tables list the assessor's statistical analysis results:

Statistical Results for PDI- Calculated by Assessor:

PDI Summary											
	Mean		Variability (%CV)							Mean Ratio (T/R)	
			Within Lot (n=10)					Between Lot (n=5)	Total (n=300)		
	Arith	Geo	Lot 1	Lot 2	Lot 3	Lot 4	Lot 5			Arith (n=60)	Geo (n=60)
TEST	(b)(4)									1.03	1.03
REF											

(b)(4)

[22] GDRP, Ferric Oxyhydroxide Intravenous Injectable NDA 021135 Revision PSG, Ferric oxyhydroxide intravenous injectable NDA 021135 Review RV - Not Archive, 05/27/2021 https://panorama.fda.gov/task/view?ID=5c7d8e6900142a80731733eed3152a33

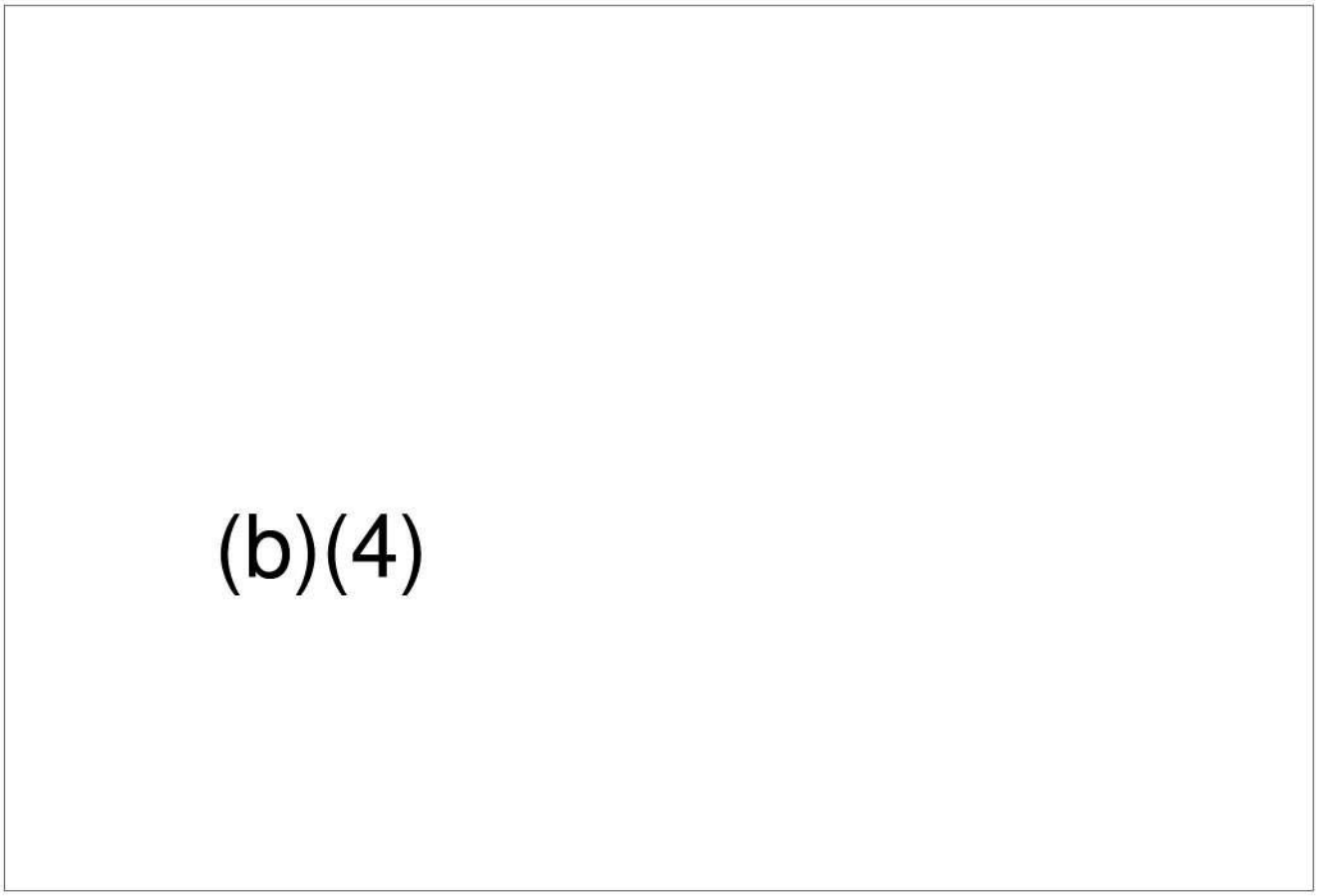
Statistical Results for D50 (volume based)- Calculated by Assessor:

D_{50} Summary											
	Mean		Variability (%CV)							Mean Ratio (T/R)	
			Within Lot (n=10)					Between Lot (n=5)	Total (n=300)		
	Arith	Geo	Lot 1	Lot 2	Lot 3	Lot 4	Lot 5			Arith (n=60)	Geo (n=60)
TEST	(b)(4)									0.95	0.95
REF											

(b)(4)

Statistical Results for SPAN (Volume based) - Calculated by Assessor:

Span Summary											
	Mean		Variability (%CV)							Mean Ratio (T/R)	
			Within Lot (n=10)					Between Lot (n=5)	Total (n=300)		
	Arith	Geo	Lot 1	Lot 2	Lot 3	Lot 4	Lot 5			Arith (n=60)	Geo (n=60)
TEST	(b)(4)									1.00	1.00
REF											



- In the original submission, the applicant results are reported as average of two (2) measurements for each preparation (see table below). Per the applicant analysis the upper bound of 95% CI for D50, SPAN, PDI and Z-avg all met the BE acceptance criteria (95% upper confidence bound ≤ 0). However, the assessor PBE analysis results for D50, SPAN and PDI are not from average of two (2) measurements for each preparation instead used individual two measurements per preparation. Based on the applicant's and assessor's PBE analysis results on the PSD study, the upper bound of 95% CI for D50, SPAN and PDI all met the BE acceptance criteria.

(b)(4)

Conclusion: PSD study# IRSUS_PRT_DLS_IVC_V03 meet PBE acceptance criteria for PDI.

The applicant's response to deficiency #4 is adequate.

5 APPENDIX

SAS Output:

Study	SAS Data	SAS Code	SAS Output/Table
Particle Size Analysis	A212340 PBE.xlsx psd raw data.xlsx	A212340 PBE.sas	DSD_D50.doc DSD_SPAN.doc PDI.doc

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	212340
APPLICANT:	Sandoz Inc.
DRUG PRODUCT:	Iron Sucrose Injection USP, 50 mg/2.5mL, 100 mg/5mL, 200 mg/10mL (Eq. 20 mg base/mL)

The Division of Bioequivalence III (DBIII) has completed its review of your submission acknowledged on the cover sheet and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if chemistry, manufacturing and controls, microbiology, labeling, or other scientific, regulatory or inspectional issues or concerns arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

FDA publishes new and revised product-specific guidances describing the Agency's current recommendations on demonstrating bioequivalence and certain other approval requirements. To ensure you are aware of FDA's recommendations for the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence (21 CFR 320.24(a)), please continue to monitor for the availability of new and revised product-specific guidances in the Federal Register and on the FDA Web site at the following address: https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm .

Sincerely yours,

{See appended electronic signature page}

April C. Braddy, Ph.D., RAC
Acting Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

6 *COMPLETED ASSIGNMENT FOR 212340 ID: 45549*

Reviewer: Katragadda, Usha **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Iron Sucrose Injection, Amendment

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
45549	12/28/2020	BIO	ANDA Amendment [1]	1	1
45549	12/28/2020	Parallel	Major Amendment (original or supplement) [1.5]	1.5	1.5
45549	12/28/2020	Parallel	In Vitro Studies (Other: IVIVC, IVPT, IVRT, GSD, QCRT) (Per study for all strengths) [1]	1	1
45549	12/28/2020	Parallel	Pre-Screening [0.25]	0.25	0.25

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	212340	
Drug Product Name	Iron Sucrose Injection [a]	
Strength(s)	EQ 20 mg Iron/mL (EQ 50 mg Iron/2.5 mL, EQ 100 mg Iron/5 mL, and EQ 200 mg Iron/10 mL)	
Applicant Name	Sandoz Inc.	
Applicant Address	100 College Road West, Princeton, NJ 08540	
US Contact Name and US Mailing Address	Gregory Seitz, Director, Regulatory Affairs	
US Contact Telephone Number	(b)(6)	
US Contact Fax Number	973-781-3710	
Original Submission Date(s)	08/29/2019 Original	
Submission Date(s) of Amendment(s) Under Review	04/16/2020 DRL response 12/28/2020 CRL response [b]	
Primary Reviewer	Ja Hye Myung, Ph.D.	
Secondary Reviewer	Moheb H. Makary, Ph.D.	
Study Number(s)	**RFR-P5-709**	**IRSUS_REP DLS_IVC_V03**
Study Type(s)	Fasting	In Vitro BE (Particle Size Distribution)
Strength(s)	EQ 100 mg Iron/5 mL	EQ 100 mg Iron/5 mL
Clinical Site	Algorithme Pharma Inc.	Not applicable
Clinical Site Address	1200 Beaumont Ave., Mount-Royal, Quebec, Canada H3P 3P1	Not applicable
Analytical Site	(b)(4)	
Analytical Site Address		
Office of Study Integrity and Surveillance (OSIS) status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☐ **Complete** ☐ **N/A**	**Post October 1, 2014 ANDAs** ☐ **Pending** ☐ **Pending for Cause Inspection** ☒ **Complete** ☐ **N/A**
Waiver/Deem Bioequivalent	☐ **Granted** ☐ **Tentatively granted** ☒ **Not granted** ☐ **N/A**	
QC Dissolution	☐ **Pending** ☐ **Adequate** ☐ **Inadequate** ☒ **N/A**	
Formulation	☐ **Adequate** ☒ **Inadequate**	

Will Response to CR Result in a Reformulation?	**☒ Possibly ☐ No ☐ N/A**		
Deficiency Classification	**☒ Major** **☐ Minor** **☐ N/A**		
Major Deficiency Theme	Inadequate formulation		
Justification for Major Designation	The bioequivalence deficiency has been classified as MAJOR because the deficiency pertains to inadequate formulation (i.e., Test and RLD not considered qualitatively (Q1) and quantitatively (Q2) the same) as noted in Appendix A, Section B.1.1 of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). The review of the response will require, in FDA's judgment, a substantial expenditure of FDA resources.		
Overall Review Result	**☐ Adequate ☒ Inadequate**		
Product Specific Guidance (PSG) Referenced in Review	**☒ Recommended/Latest Revision Date: Sep 2021** **RLD/RS Number: N021135** **☐ N/A**		
Revised/New Draft Guidance Generated as Part of Current Review	**☐ YES ☒ NO**		
Bioequivalence study tracking/supporting document #	**Study/ test type**	**Strength**	**Review Result**
#1, 6, and 9	**Fasting**	**EQ 100 mg Iron/5 mL**	**☐ Adequate ☒ Inadequate**
#1, 6, and 9	**In Vitro (particle size distribution)**	**EQ 100 mg Iron/5 mL**	**☐ Adequate ☒ Inadequate**
#1, 6, and 9	**Waivers**	**EQ 50 mg Iron/2.5 mL and EQ 200 mg Iron/10 mL**	**☐ Adequate ☒ Inadequate**

[a] Based on a citizen petition (Docket #FDA-2005-P-0319, see Section 3.3), API name has been changed from "Iron Sucrose" to "Ferric Oxyhydroxide". The old API name "Iron Sucrose" is used in the current assessment since the applicant has used it in the original submission.

[a] Bioequivalence CRL response dated 12/28/2020 refers to the applicant Bioequivalence DRL response dated 04/16/2020.

[c] There are several different reference drugs that use the active ingredient, ferric oxyhydroxide (e.g., Venofer, Ferrlecit, INFED, and [redacted] The current ANDA under review is referencing Venofer® (ferric oxyhydroxide) Injection.

ADDENDUM TO BIOEQUIVALENCE REVIEW

This is an addendum to the amendment bioequivalence (BE) review of ANDA 212340 finalized on 08/12/2021.[1] The purpose of this addendum is to inform a formulation deficiency additionally found during the amendment BE review to the applicant, which has been reviewed by the Office of Generic Drug Policy (OGDP, see Attachment 1).

Although the corresponding reference listed drug (RLD, NDA 021135) lists the drug product excipients to be [redacted] and Water for injection only,[2] based on the response to CP FDA-2016-P-1163, for the purposes of qualitative and quantitative sameness (Q1/Q2) for the purposes of 314.94(a)(9)(iv), the agency considers NDA 021135 to contain the inactive ingredients, sucrose (Q.S. to 300 mg/mL), [redacted] and [redacted].[3,4,5]

As per the Office of Pharmaceutical Quality (OPQ)'s drug product review for the current application (ANDA 212340, see Attachment 2),[6,7] [redacted] Thus, the applicant's test formulation for ANDA 212340 is not Q1/Q2 the same as the RLD.

In line with previous a similar case for ANDA 208977,[8] the applicant will be informed that the proposed formulation provided in Module 3.2.P.1 is not qualitatively and quantitatively the same to the RLD with respect to one or more inactive ingredients. Also, it is recommended that the applicant reviews the Agency's response on Citizen Petition [Docket ID: FDA- 2016-P-1163] and, if appropriate, revises the API and inactive ingredients in their ANDA application.

---

[1] Panorama, ANDA-212340-ORIG-1-AMEND-9, Bioequivalence Review, A212340N000DB-Review01-Amend12282020.pdf, Reviewer: Usha Katragadda, 08/12/2021; https://panorama.fda.gov/task/view?ID=5fecbfda00de004de0a05eab1f8f1710

[2] DocuBridge, NDA# 021135, #0202(690) 01/07/2019, Module 3.2.P.3.3 Description and Composition of the Drug Product; \\CDSESUB1\evsprod\nda021135\0202\m3\32-body-data\32p-drug-prod\venofer-iron-sucrose-i-20-mgml-injectable-luitpold-pharmaceutica\32p3-manuf\formulation-master-2340-600l.pdf

[3] GDRP: A208977 Drug Product-R04 AQ Final Date: 7/12/22

[4] R:\OGDS11\DIVISION\BIO\BIO1\Email Reference\208977 Iron Sucrose Injection\ RE Q1Q2 documentation for RLD table - start of draft (ANDA 208977).msg

[5] R:\OGDS11\DIVISION\BIO\BIO1\Email Reference\208977 Iron Sucrose Injection\ Q1Q2 documentation for RLD table - start of draft .msg

[6] Panorama, ANDA-212340-ORIG-1-AMEND-9, Drug Product Quality Review, Reviewer: Dahui Liu, A212340 Drug Product R02b-IQ.docx; https://panorama.fda.gov/task/view?ID=5fecbfda00de02508b9c590a6ba7295f

[7] R:\OGDS11\DIVISION\BIO\BIO3\Email Communications\ANDA 212340 Iron Sucrose Injection\A212340_email communication with OPQ_NaCl in drug product.pdf

[8] Panorama, ANDA-208977-ORIG-1-AMEND-23, Bioequivalence Discipline Review, Reviewer: Tian Zhou; https://panorama.fda.gov/task/view?ID=6259a72f011886fa384481c194dd5246

To capture the formulation deficiency, the following deficiency will be sent to the applicant:

Foley Hoag LLP submitted a Citizen Petition [Docket ID: FDA- 2016-P-1163] requesting, among other things, that FDA recognize that Velphoro (new drug application (NDA) 205109) is eligible for 5-year new chemical entity (NCE) exclusivity under 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the Federal, Food, Drug, and Cosmetic Act (FD&C Act) (Velphoro Citizen Petition). The Agency's response dated May 26, 2021 also states that "ferric oxyhydroxide is responsible for the pharmacological activity of both Velphoro and Venofer, and is thus the active ingredient in both drug products under the regulatory definition of "active ingredient" and additionally, "[s]ucrose and starches are merely excipients providing stability and processes functions…" (Reference: FDA Letter Response to Citizen Petition (CP), Docket No FDA-2016-P-1163, at 40 (May 26, 2021) (Velphoro Petition Response), available at: https://downloads.regulations.gov/FDA-2016-P-1163-0097/attachment_1.pdf).

Accordingly, we recommend you review the Agency's response and make any appropriate revisions to your application regarding active pharmaceutical ingredient (API) and inactive ingredients. Your proposed formulation provided in Module 3.2.P.1 is not qualitatively and quantitatively the same to the reference listed drug (RLD) with respect to one or more inactive ingredients.

Thus, the application is now considered **inadequate**.

Attachments

1. e-mail discussion with OGDP team regarding the formulation deficiency

The language of formulation deficiency was consulted with OGDP team via emails. The following e-mail communication with OGDP is located in R drive: [9]

A212340_email communication with C

2. e-mail discussion with OPQ review team regarding the presence of NaCl in the drug product

The (b)(4) the current application was consulted with OPQ team via emails. The following e-mail communication with OPQ is located in R drive: [10]

A212340_email communication with C

[9] R:\OGDS11\DIVISION\BIO\BIO3\Email Communications\ANDA 212340 Iron Sucrose Injection\A212340_email communication with OGDP_formulation deficiency.pdf

[10] R:\OGDS11\DIVISION\BIO\BIO3\Email Communications\ANDA 212340 Iron Sucrose Injection\A212340_email communication with OPQ_NaCl in drug product.pdf

NOTE TO REGULATORY PROJECT MANAGER: As of 02/21/2023, there are three policy alerts from OGDP related to Iron Sucrose Injection (Docket #FDA-2020-P-0158, #FDA-2021-P-0893, and #FDA-2005-P-0319 (2005P-0095), for Venofer® (ferric oxyhydroxide) Injection (NDA 021135)).

No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead. No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL for Bioequivalence or Quality.

The deficiency letter in the current bioequivalence addendum review supersedes the letter at the end of the bioequivalence review, which is located in GDRP [GDRP, ANDA-212340-ORIG-1-AMEND-9, Bioequivalence Discipline Review, A212340N000DB-Review01-Amend12282020.pdf, Completed on 08/12/2021].

BIOEQUIVALENCE DEFICIENCY TO BE PROVIDED TO THE APPLICANT

ANDA:	212340
APPLICANT:	Sandoz Inc.
DRUG PRODUCT:	Iron Sucrose Injection, EQ 20 mg Iron/mL

The Division of Bioequivalence III (DBIII) has completed its review of your submission acknowledged on the cover sheet and has identified the following deficiency:

Deficiency Related to the Test Formulation

Foley Hoag LLP submitted a Citizen Petition [Docket ID: FDA- 2016-P-1163] requesting, among other things, that FDA recognize that Velphoro (new drug application (NDA) 205109) is eligible for 5-year new chemical entity (NCE) exclusivity under 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the Federal, Food, Drug, and Cosmetic Act (FD&C Act) (Velphoro Citizen Petition). The Agency's response dated May 26, 2021 also states that "ferric oxyhydroxide is responsible for the pharmacological activity of both Velphoro and Venofer, and is thus the active ingredient in both drug products under the regulatory definition of "active ingredient" and additionally, "[s]ucrose and starches are merely excipients providing stability and processes functions…" (Reference: FDA Letter Response to Citizen Petition (CP), Docket No FDA-2016-P-1163, at 40 (May 26, 2021) (Velphoro Petition Response), available at: https://downloads.regulations.gov/FDA-2016-P-1163-0097/attachment_1.pdf).

Accordingly, we recommend you review the Agency's response and make any appropriate revisions to your application regarding active pharmaceutical ingredient (API) and inactive ingredients. Your proposed formulation provided in Module 3.2.P.1 is not qualitatively and quantitatively the same to the reference listed drug (RLD) with respect to one or more inactive ingredients.

Sincerely yours,

{See appended electronic signature page}

April C. Braddy, Ph.D., RAC
Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

COMPLETED ASSIGNMENT FOR 212340 ID: 50465

Reviewer: Myung, Ja Hye **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: A212340-Addendum-Iron Sucrose Injection, EQ 100 mg Iron/5 mL

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*		
50465	12/28/2020	Parallel2023	Other (Addendum not for error correction) (0.5 per application) [0.5]	0.5	0.5	Edit	Delete

DIVISION OF BIOEQUIVALENCE REVIEW - ADDENDUM

ANDA No.	212340	
Drug Product Name	Iron Sucrose Injection, USP	
Strength(s)	Eq. 20 mg base/mL (50 mg/2.5 mL, 100 mg/5 mL, 200 mg/10 mL)	
Applicant Name	Sandoz Inc.	
Applicant Address	100 College Road West Princeton, NJ 08540	
US Contact Name	Gregory Seitz, Director Regulatory Affairs	
US Contact Telephone Number	(b)(6)	
US Contact Fax Number	(973) 781-3710	
Original Submission Date(s)	8/29/2019 (Original Submission)	
Submission Date(s) of Amendment(s) Under Review	N/A	
Primary Reviewer	Yun Wang, Ph.D.	
Secondary Reviewer	Moheb Makary, Ph.D.	
Tertiary Reviewer	Ke Ren, Ph.D.	
Study Number(s)	RFR-P5-709	IRSUS_REP DLS_IVC_V03
Study Type(s)	Fasting (Pivotal)	In vitro BE (Particle size distribution)
Strength(s)	1 x 100 mg/5 mL	1 x 100 mg/5 mL
Clinical Site	Algorithme Pharma Inc.	N/A
Clinical Site Address	1200 Beaumont Ave. Mount-Royal, Quebec, Canada H3P 3P1	N/A
Analytical Site	(b)(4)	
Analytical Site Address		
OSIS status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☐ **Complete** ☐ **N/A (Waiver/Deem Bioequivalent)**	**Post October 1, 2014 ANDAs** ☐ **Pending** ☐ **Pending For Cause Inspection** ☒ **Complete** ☐ **N/A**

Waiver	☐ **Granted** ☐ **Tentatively granted** ☒ **Not granted** ☐ **N/A**		
QC Dissolution	☐ **Pending** ☐ **Adequate** ☐ **Inadequate** ☒ **N/A**		
Formulation	☒ **Adequate** ☐ **Inadequate**		
Will Response to CR Result in a Reformulation?	☐ **Possibly** ☐ **No** ☒ **N/A**		
Deficiency Classification	☒ **Major** ☐ **Minor/IR** ☐ **N/A**		
Major Deficiency Theme	Insufficient pre-study method validation data for particle size distribution (PSD) study		
Justification for Major Designation	The bioequivalence deficiencies have been classified as MAJOR because the deficiencies pertain to insufficient method validation data as noted in Appendix A, Section B.1.a of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). The review of the response will require, in FDA's judgment, a substantial expenditure of FDA resources.		
Overall Review Result	☐ **Adequate** ☒ **Inadequate**		
Product Specific Guidance (PSG) Referenced in Review	☒ **Recommended/Latest Revision Date: Nov, 2013** **RLD/RS Number: 021135**[1] ☐ **N/A (no PSG available at time of review)**		
Revised/New Draft Guidance Generated as Part of Current Review	☐ **YES** ☒ **NO**		
Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**
1	**Fasting**	100 mg/5 mL	☐ **Adequate** ☒ **Inadequate**
1	**In vitro (Particle Size Distribution)**	100 mg/5 mL	☐ **Adequate** ☒ **Inadequate**
1	**Waivers**	50 mg/2.5 mL and 200 mg/10 mL	☐ **Adequate** ☒ **Inadequate**

[1] https://www.accessdata.fda.gov/drugsatfda_docs/psg/Iron_sucrose_inj_21135_RV11-13.pdf

ADDENDUM TO BIOEQUIVALENCE REVIEW

1 EXECUTIVE SUMMARY

This is an addendum to the previous bioequivalence (BE) review.[2]

This addendum has been created to update Section 4.2 Formulation Data in the original BE review in addition to the Office of Study Integrity and Surveillance (OSIS) status for in vitro BE study. Based on internal Agency discussion on Friday January 4, 2019, it was determined that in order to maintain consistency with the handling of Velphoro ANDA reviews, that ferric oxyhydroxide is considered to be the active pharmaceutical ingredient (API) of Iron Sucrose[3]. Therefore, per the reference-listed drug (RLD) component and composition table, the excipients of Venofer® (iron sucrose) Injection are **sucrose**, sodium hydroxide (used as pH adjuster), and water (please see test and reference product formulations in the appendix). The test product formulation in current ANDA is compared with reference product as below.

Formulation Comparison between Test and RLD

Ingredient name and standard	ANDA's formula	RLD Venofer® (Iron Sucrose Injection, USP)	Function in Formulation	Difference between T and R in %
(b)(4)				

Per RLD labeling[6], "*The drug product contains **approximately** 30% sucrose w/v (300 mg/mL) and has a pH of 10.5 to 11.1.*" Previously, the applicant submitted a controlled correspondence 139879 to request verification of the acceptability of the qualitative (Q1) and quantitative (Q2) sameness of its formulation with the FDA[7]. The applicant proposed (b)(4) of sucrose in its test product, and the test formulation was deemed Q1 and Q2 the same as the reference product.

[2] GDRP, AND-212340-ORIG-1, Bioequivalence Discipline Review, Yun Wang (4), Final Date: 2/18/2020

(b)(4)

[4] In page 53/586 of the pharmaceutical development report, the applicant mentioned that the nominal content of sucrose is 300 mg/mL. \\cdsesub1\evsprod\anda212340\0001\m3\32-body-data\32p-drug-prod\iron-sucrose-injection-rafarm-sa\32p2-pharm-dev\pharmaceutical-development.pdf

(b)(4)

[6] RLD VENOFER® label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021135s035lbl.pdf

[7] https://panorama.fda.gov/task/view?ID=5d8a38b30050beeafe83cdf12f1b0110

In the test product certificate of analysis (COA) of the current submission[8], the specification for sucrose content is set as [redacted] for the 50 mg/2.5 ml, 100 mg/5ml, and 200 mg/10ml. The sucrose content for the test product,100 mg/5mL Lot #801859 (bio-lot), 801863, and 801869, is [redacted] respectively. The sucrose content for the test product, 50 mg/2.5 mL Lot #801852, 801856, and 801864, is [redacted] respectively. The sucrose content for the test product, [redacted] Lot #801865, 801866, and 801868, is [redacted], respectively. The applicant also conducted Q1/Q2 testing for their test product and reference product as listed below[9]. The sucrose content in the test product is comparable with reference product (maximum difference [redacted]%). Thus, the formulation of the test and reference products are Q1/Q2 the same. The test product formulation remains acceptable.

(b)(4)

Per the original BE review[10], the applicant's fasting study is **inadequate** due to bioanalytical deficiency. Per draft product specific BE guidance for iron sucrose Injection[11], the applicant also conducted the *in vitro* particle size distribution test by Dynamic Light Scattering. The particle size distribution testing is **inadequate** due to multiple deficiencies related to method validation.

The formulations for the 50 mg/2.5 mL and 200 mg/10 mL strengths are proportionally similar to the bio-strength 100 mg/5 mL which underwent BE testing. However, the waiver request is not granted due to inadequate BE study on the 100 mg/5 mL strength.

Please refer to Section 3.6 of original BE review for OSIS Status for in vivo PK study [12]. For in vitro BE study, the inspection outcomes were pending at the time of original review completion. Per the EIR[13], the inspection at in vitro BE study site ([redacted]) is classified as No Action Indicated (NAI). In addition, the study submitted in the current ANDA does not indicate any

[8] GDRP, AND-212340-ORIG-1, 8/28/2019, 3.2.P.5.4 Batch Analysis
[9] GDRP, AND-212340-ORIG-1, Drug Product Review, Dahui Liu, 2/26/2020
[10] GDRP, AND-212340-ORIG-1, Bioequivalence Discipline Review, Yun Wang (4), Final Date: 2/18/2020
[11] https://www.accessdata.fda.gov/drugsatfda_docs/psg/Iron_sucrose_inj_21135_RV11-13.pdf
[12] GDRP, AND-212340-ORIG-1, Bioequivalence Discipline Review, Yun Wang (4), Final Date: 2/18/2020
[13] GDRP, AND-212340-ORIG-1, Site: [redacted], EIR Review Rapharm Greece.pdf, Date: 4/8/2020

conduct issues and no data integrity deficiencies were identified by the reviewer. The OSIS inspection status of the current ANDA is complete.

The application remains **inadequate** with deficiencies.

The BE letter at the end of the original review remains unchanged. Since the previous BE deficiencies have been communicated to the firm on February 14, 2020 and no new deficiency has been identified in this addendum, no communication to the firm is necessary at this time.

Appendix

Test Formulation[14]

Unit Dose Composition of Iron Sucrose Injection, 50mg/2.5mL:

Ingredient	Function	Amount per mL	Amount per vial	% w/v	IIG[1] Limit (Injection)
Iron Sucrose	Active Pharmaceutical Ingredient	20 mg elemental iron	(b)(4)		
Sodium Hydroxide, NF	pH adjustment	q.s. to pH 10.5 – 11.1			
Water for Injection, USP					

Unit Dose Composition of Iron Sucrose Injection, 100mg/5mL:

Ingredient	Function	Amount per mL	Amount per vial	% w/v	IIG[1] Limit (Injection)
Iron Sucrose	Active Pharmaceutical Ingredient	20 mg elemental iron	(b)(4)		
Sodium Hydroxide, NF	pH Adjustment	q.s. to pH 10.5 – 11.1			
Water for Injection, USP					

Unit Dose Composition of Iron Sucrose Injection, 200mg/10mL:

Ingredient	Function	Amount per mL	Amount per vial	% w/v	IIG[1] Limit (Injection)
Iron Sucrose	Active Pharmaceutical Ingredient	20 mg elemental iron	(b)(4)		
Sodium Hydroxide, NF	pH Adjustment	q.s. to pH 10.5 – 11.1			
Water for Injection, USP					

[14] GDRP, ANDA 212340, Module 3.2.P.1, Description and Composition of the Drug Product

(b)(4)

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	212340	
Drug Product Name	Iron Sucrose Injection, USP	
Strength(s)	Eq. 20 mg base/mL (50 mg/2.5 mL, 100 mg/5 mL, 200 mg/10 mL)	
Applicant Name	Sandoz Inc.	
Applicant Address	100 College Road West Princeton, NJ 08540	
US Contact Name	Gregory Seitz, Director Regulatory Affairs	
US Contact Telephone Number	(b)(6)	
US Contact Fax Number	(973) 781-3710	
Original Submission Date(s)	8/29/2019 (Original Submission)	
Submission Date(s) of Amendment(s) Under Review	N/A	
Primary Reviewer	Yun Wang, Ph.D.	
Secondary Reviewer	Moheb Makary, Ph.D.	
Tertiary Reviewer	Ke Ren, Ph.D.	
Study Number(s)	RFR-P5-709	IRSUS_REP DLS_IVC_V03
Study Type(s)	Fasting (Pivotal)	In vitro BE (Particle size distribution)
Strength(s)	1 x 100 mg/5 mL	1 x 100 mg/5 mL
Clinical Site	Algorithme Pharma Inc.	N/A
Clinical Site Address	1200 Beaumont Ave. Mount-Royal, Quebec, Canada H3P 3P1	N/A
Analytical Site	(b)(4)	
Analytical Site Address		
OSIS status	**Backlog, Year 1 and Year 2 ANDAs**	**Post October 1, 2014 ANDAs** **☒ Pending (for in vitro site)**

	☐ Pending ☐ Complete ☐ N/A (Waiver/Deem Bioequivalent)	☐ Pending For Cause Inspection ☒ Complete (for in vivo clinic and analytical sites) ☐ N/A	
Waiver	☐ Granted ☐ Tentatively granted ☒ Not granted ☐ N/A		
QC Dissolution	☐ Pending ☐ Adequate ☐ Inadequate ☒ N/A		
Formulation	☒ Adequate ☐ Inadequate		
Will Response to CR Result in a Reformulation?	☐ Possibly ☐ No ☒ N/A		
Deficiency Classification	☒ Major ☐ Minor/IR ☐ N/A		
Major Deficiency Theme	Insufficient pre-study method validation data for particle size distribution (PSD) study		
Justification for Major Designation	The bioequivalence deficiencies have been classified as MAJOR because the deficiencies pertain to insufficient method validation data as noted in Appendix A, Section B.1.a of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). The review of the response will require, in FDA's judgment, a substantial expenditure of FDA resources.		
Overall Review Result	☐ Adequate ☒ Inadequate		
Product Specific Guidance (PSG) Referenced in Review	☒ Recommended/Latest Revision Date: Nov, 2013 RLD/RS Number: 021135[1] ☐ N/A (no PSG available at time of review)		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**
1	**Fasting**	100 mg/5 mL	☐ Adequate ☒ Inadequate
1	**In vitro (Particle Size Distribution)**	100 mg/5 mL	☐ Adequate ☒ Inadequate
1	**Waivers**	50 mg/2.5 mL and 200 mg/10 mL	☐ Adequate ☒ Inadequate

[1] https://www.accessdata.fda.gov/drugsatfda_docs/psg/Iron_sucrose_inj_21135_RV11-13.pdf

1 EXECUTIVE SUMMARY

This application contains the results of a fasting bioequivalence (BE) study comparing a test product, Sandoz Inc.'s Iron Sucrose Injection, Eq. 20 mg base/mL, to the corresponding reference product, American Regent Inc's Venofer® (iron sucrose) Injection, EQ 100 mg Iron/5 mL (EQ 20 mg Iron/mL). The BE study was designed as a single-dose, two-treatment, fourteen-group, parallel study in healthy male and female subjects.

The current draft product specific BE guidance for Iron Sucrose Injection recommends measure total iron (TI) and transferrin-bound iron (TBI) concentration in serum. There is no need to perform baseline correction for both analytes. BE is based on the 90% confidence interval of 1) Maximum value of the difference in concentration between Total Iron and Transferrin-bound Iron over all time points measured; and 2) Difference in AUC between Total Iron and Transferrin-bound Iron. AUC should be calculated separately to maximize the number of data points used in cases of missing data[2]. In addition, the test product should be qualitatively (Q1) and quantitatively (Q2) the same to the reference-listed drug (RLD) and sameness in physicochemical properties need to be established between the test product and RLD.

Based on assessor's calculation, the *in vivo* fasting BE study results are summarized in the table below.

Iron Sucrose USP Injection (No of subjects completed = 200) Dose: 1 x 100 mg Least Squares Geometric Means*, Ratio of Means (%), and 90% Confidence Intervals (%)							
Pivotal Fasted Bioequivalence Study (Study No.RFR-P5-709)							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *µg/dl)	5548.15	100	6367.12	100	0.87	81.92	92.68
AUC∞ (hr *µg/dl)	5983.54	85*+	6836.95	82*+	0.88	81.54	93.93
Cmax (µg/dl)	2194.26	100	2476.06	100	0.89	85.04	92.35

+The following subjects are excluded from AUCi calculation due to nonlinear elimination phase or missing samples. **TI**: Test: Subject Nos. (b)(6)
TBI: Test: Subject Nos. (b)(6); Ref: Subject Nos. (b)(6) (b)(6)
The final subject exclusion will be: **Test (15)**: (b)(6)
Ref (18): Subject Nos. (b)(6)

Subjects were dosed in fourteen groups. There was no significant group*treatment interaction ($p \geq 0.10$) for all PK parameters (lnAUCt: p=0.5915; lnAUCi: p=0.6240;

[2] https://www.accessdata.fda.gov/drugsatfda_docs/psg/Iron_sucrose_inj_21135_RV11-13.pdf

lnCmax: p=0.1637). Thus, the assessor dropped the group*treatment term in the final statistical model as per the current Division of Bioequivalence (DB) practice.

The 90% CIs for the test/reference ratios of least square geometric means of LnC_{max}, $LnAUC_{0-t}$ and $LnAUC_{\infty}$ of iron sucrose-associated iron fall within the acceptance range of 80.00-125.00% in the fasting BE study (Study No. RFR-P5-709).

Due to concern to the adverse event (syncope) after receiving test product, and the fainting after catheter insertion, Division of Bioequivalence III (DBIII) sent a consult to Division of Clinical Review (DCR) for any safety concern of the test product[3]. Based on consult response from the DCR[4], the noted two adverse events of fainting were more likely due to vaso-vagal syncope which is commonly seen in a younger population, due to many triggers, including catheter insertion. Hence it does not indicate any safety or quality concern for the test product (please see detail discussion in Section 4.1.1.2.3 and DCR consult attached in Section 4.3.2). However, the applicant's fasting study is **inadequate** due to bioanalytical deficiency.

The applicant also submitted the results of pilot fasting BE study (No. RFR-P5-810) comparing test product, Sandoz's Iron Sucrose Injection, 100 mg/5 mL to the corresponding reference product, American Regent Inc, USA's Iron Sucrose Injection, 100 mg/5 mL. The pilot BE study was designed as a single-dose, three-arm parallel study in healthy male and female subjects. For Test product-1, the 90% CI for test/reference ratios of the least square geometric means of LnAUCt and LnCmax both met BE limits of 80.00-125.00%. The LnAUCi for Test-1 met BE criteria only after excluding subjects with AUCt/AUCi < 0.8 for TI or TBI. Based on the applicant and reviewer's calculations, Test product-2 failed to demonstrate BE to the reference product for all three PK parameters. Please see details of pilot study in Section 4.3.1 and DBIII's response to consult request in the pre-ANDA meeting[5]

The formulation of the test and reference products are Q1/Q2 the same. The test formulation is acceptable. The formulations for 50 mg/2.5 mL and 200 mg/10 mL strengths are proportionally similar to the bio-strength 100 mg/5 mL which underwent BE testing. However, the waiver request is not granted due to inadequate BE study on the 100 mg/5 mL strength.

Per draft product specific BE guidance for iron sucrose Injection, the firm also conducted the *in vitro* particle size distribution test by Dynamic Light Scattering. The particle size distribution testing is **inadequate** due to the deficiency related to method validation.

Please refer to Section 3.6 for OSIS Status.

The application is **inadequate** with deficiencies.

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[3] GDRP, ANDA 212340-ORIG-1, Bioequivalence IR and Consults, Yun Wang (4), 11/13/2019
[4] GDRP, ANDA 212340-Bioequivalence IR and Consults, Respond to Consult Request, 1/29/2020
[5] GDRP, ANDA 212340-PDEV-Meeting-00197, Respond to Consult Request, Yun Wang (4), 11/29/2018

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3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Drug Product and Strengths	Iron Sucrose Injection, USP, Eq. 20 mg base/mL (50 mg/2.5 mL, 100 mg/5 mL, 200 mg/10 mL)
Reference Standard (RS) and Strength	VENOFER® (iron sucrose) Injection, Eq 20 mg base/mL (100 mg/5 mL)
RS Holder; NDA Number; Approval Date[6]	American Regent Inc, NDA 021135, Nov 6, 2000
Reference Listed Drug (RLD) and Strength	VENOFER® (iron sucrose) Injection, Eq. 20 mg base/mL (50 mg/2.5 mL, 100 mg/5 mL, 200 mg/10 mL)
RLD Holder; NDA Number; Approval Date[7]	American Regent Inc, NDA 021135, EQ 50 mg base/2.5 mL: Mar 20, 2005, EQ 100 mg base/5 mL: Nov 6, 2000, EQ 200 mg base/10 mL: Feb 9, 2007

3.2 PK/PD Information[8]

Most recent RLD label (provide embedded document)	 021135s035l
Indication	Venofer is an iron replacement product indicated for the treatment of iron deficiency anemia in patients with chronic kidney disease (CKD).
Boxed warning	N/A
Bioavailability	In healthy adults administered intravenous doses of Venofer, its iron component exhibited first order kinetics with an elimination half-life of 6 h, total clearance of 1.2 L/h, and steady state apparent volume of distribution of 7.9 L. The iron component appeared to distribute mainly in blood and to some extent in extravascular fluid. A study evaluating Venofer containing 100 mg of iron labeled with $^{52}Fe/^{59}Fe$ in patients with iron deficiency showed that a significant amount of the administered iron is distributed to the liver, spleen and bone marrow and that the bone marrow is an irreversible iron trapping compartment.
Food Effect	RLD labeling does not mention effect of food on pharmacokinetics.

[6] Per Orange Book
[7] Electronic Orange Book, Search: Iron Sucrose, Last access date: 12/6/2019.
[8] RLD VENOFER® label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021135s035lbl.pdf

Tmax	N/A
Metabolism	Following intravenous administration of Venofer, iron sucrose is dissociated into iron and sucrose.
Excretion	The sucrose component is eliminated mainly by urinary excretion. In a study evaluating a single intravenous dose of Venofer containing 1,510 mg of sucrose and 100 mg of iron in 12 healthy adults (9 female, 3 male: age range 32 to 52), 68.3% of the sucrose was eliminated in urine in 4 h and 75.4% in 24 h. Some iron was also eliminated in the urine. In this study and another study evaluating a single intravenous dose of iron sucrose containing 500 to 700 mg of iron in 26 patients with anemia on erythropoietin therapy (23 female, 3 male; age range 16 to 60), approximately 5% of the iron was eliminated in urine in 24 h at each dose level.
Half-life	6 h
Maximum Daily Dose	400 mg in Adult Patients with Peritoneal Dialysis Dependent-Chronic Kidney Disease (PDD-CKD).

3.3 OGD Recommendations for Drug Product

Source of most recent recommendations or provide the embedded document to the current draft guidance	The current BE recommendations for the drug product are listed in the draft product specific guidance (recommended November 2013). https://www.accessdata.fda.gov/drugsatfda_docs/psg/Iron_sucrose_inj_21135_RV11-13.pdf	
Summary of OGD or DB History	Approved ANDAs[9]:	No
	Pending ANDAs:	Yes

[9] Orange Book, search iron sucrose, Last accessed 12/6/2019

	Controls[10]:	Yes **# 19117934:** On 11/20/2017, the applicant sent a control correspondence (CC) requesting Agency guidance on the suitability of their proposed BE and in vitro studies for demonstrating BE to the RLD Venofer®, Iron Sucrose Injection, NDA 021135. The applicant's proposed studies to demonstrate BE are based on D50 and SPAN or polydispersity index for the particle sizing study; additionally, the physicochemical properties outlined by the applicant generally follow the FDA Draft Guidance for Iron Sucrose (revised Nov 2013), with some minor omissions outlined in CC review[11]. **# 139789:** The applicant sent this CC on 4/16/2015 to request Agency to verify the acceptability of the qualitative and quantitative sameness (Q1/Q2) of its formulation for Iron Sucrose Injection, Eq. 20 mg base/mL[12].
	Protocols[13]:	Yes

[10] GDRP and http://cdsogd1/controls/DOCGRID.ASP, Last accessed: 12/6/2019.
[11] file:///C:/Users/Yun.Wang4/Downloads/CC_19117934%20Review.pdf
[12] https://panorama.fda.gov/task/view?ID=5530eacd00b948b929ca59ff003e0c92
[13] http://fdswv04385/seltrack/Protocols.asp, Last accessed: 12/6/2019.

	Pending Citizen Petitions and other legal and regulatory issues:[14] If yes, please comment.	☒ Yes ☐ No 1. FDA-2005-P-0319 Requests FDA to require identical manufacturing process, physico-chemical properties, BE standards. Between April 2006 and July 2012, Luitpold submitted a total of 5 supplemental petitions. FDA has not yet responded to the Citizen Petition[15]. Per OGD policy alert list dated 1/21/2020[16], no approved actions can be taken and no CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL for BE or quality. 2. FDA-2020-P-0158 1) Issue guidance, and publicly affirm, that the ANDA approval pathway is not appropriate for harder-to-copy complex drugs already identified by FDA; 2) FDA's planned guidance on therapeutic equivalence for follow-on drugs approved pursuant to Section 505(b)(2)4 make clear that a follow-on harder-to-copy complex drug may be determined to be therapeutically equivalent to its reference listed drug ("RLD"), when the two drugs meet the existing criteria, namely, they have: (1) the same active ingredient; (2) the same route of administration, Per OGD policy alert list dated 1/21/2020[17], no CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL for Filing or Quality

[14] http://sharepoint.fda.gov/orgs/CDER-OGD/OGDP/DLRS/SitePages/Home.aspx
[15] Current OGD draft consult on FDA-2005-P-0319 is located in Panorama project 8030529, Citizen Petition Consult: FDA-2005-P-0319 Iron Sucrose Injection (Venofer) Luitpold Pharmaceuticals
[16] http://sharepoint.fda.gov/orgs/CDER-OGD/OGDP/OGDPAL/SitePages/Home.aspx
[17] http://sharepoint.fda.gov/orgs/CDER-OGD/OGDP/OGDPAL/SitePages/Home.aspx

Special considerations as listed in the current draft product specific BE guidance[18]:

1. The proposed parenteral drug product should be qualitatively (Q1) and quantitatively (Q2) the same as the RLD. Equivalence in the stoichiometric ratios of iron, sucrose, and other relevant components need to be established.

2. Sameness in physicochemical properties needs to be established. These in vitro characterizations should be conducted on at least three batches of the ANDA and RLD. Attributes that should be included in the characterization are:

   • Iron core characterizations including but not limited to core size determination, iron oxide crystalline structure and iron environment.
   • Composition of carbohydrate shell and surface properties.
   • Particle morphology.
   • Labile iron determination under physiologically relevant conditions. The tests can be performed with in vitro haemodialysis system[19], the catalytic bleomycin assay of spiked human serum samples [20], the spectrophotometric measurement of Fe reduction, or other methods that are validated for accuracy and precision.

3. For additional information regarding statistical analysis of in vitro data, please refer to *Bioequivalence Recommendations for Specific Products: Budesonide Suspension (Draft)*.

3.4 Pre-Study Bioanalytical Method Validation

***In Vivo* PK Study**

Total Serum Iron (TI)

Information Requested	Data
Bioanalytical method validation report location	TTS-V2-753(R2) Validation Report TTS-V2-753(R1) was included as part of the Analytical Report RFR-P5-810(TTS); however, the present table reflects the revised validation report TTS-V2-753(R2). The bioanalytical method and the range did not change. Module 5.3.1.4
Analyte	Total Serum Iron from Iron Sucrose
Internal standard (IS)	NA (No Internal standard was used.)
Method description	(b)(4)

[18] https://www.accessdata.fda.gov/drugsatfda_docs/psg/Iron_sucrose_inj_21135_RV11-13.pdf
[19] Balakrishnan VS, *et al*. Physicochemical properties of ferumoxytol, a new intravenous iron preparation. *Eur J Clin Invest.* 2009 Jun;39(6):489-96.
[20] Burkitt MJ, *et al*. A simple, highly sensitive and improved method for the measurement of bleomycin-detectable iron: the 'catalytic iron index' and its value in the assessment of iron status in haemochromatosis. *Clin Sci (Lond).* 2001 Mar;100(3):239-47.

	(b)(4)
Limit of quantitation	50.0 µg/dL
Average recovery of drug (%)	NA (No extraction was involved.)
Average recovery of IS (%)	NA (No Internal standard was used.)
Standard curve concentrations (µg/dL)	50.0 µg/dL to 2500.0 µg/dL
QC concentrations (µg/dL)	Proxy: 50.0 µg/dL, 150.0 µg/dL, 500.0 µg/dL, 1800.0 µg/dL, 2500.0 µg/dL Human Serum: (LOQ at 58.6 µg/dL): 58.6, 206.8, 558.0, 1856.5, 2557.9 µg/dL Human Serum: (LOQ at 50.0 µg/dL): 50.0, 205.6, 556.7, 1855.2, 2556.6 µg/dL Human Serum: (LOQ at 50.0 µg/dL): 50.0, 220.2, 569.7, 1869.8, 2551.9 µg/dL
QC Intraday precision range (%)	Proxy 0.5 % to 2.6 % (Human Serum (LOQ at 50.0 µg/dL): 0.4% to 2.1%)
QC Intraday accuracy range (%)	Proxy 98.1 % to 104.0% (Human Serum (LOQ at 50.0 µg/dL): 97.0% to 102.7 %)
QC Interday precision range (%)	Proxy NA (Human Serum (LOQ at 50.0 µg/dL): 1.2% to 7.7%)
QC Interday accuracy range (%)	Proxy NA (Human Serum (LOQ at 50.0 µg/dL): 98.8% to 100.9%)
Bench-top stability (hrs)	Proxy 26.0 hours at 22°C Nominal Human Serum 25.8 hours at 22°C Nominal
Stock stability (days)	Iron Stock Stability: as per certificate of analysis Iron Sucrose Stock Stability: as per certificate of analysis Iron & Iron Sucrose Intermediate solutions: prepared fresh daily
Processed stability (hrs)	Chromophore stability information is proprietary will be share directly to HA
Freeze-thaw stability (cycles)	5 cycles
Long-term storage stability (days)	Proxy 211 days at -20ºC Nominal Human Serum 146 days at -20ºC Nominal
Dilution integrity*	Concentration 2X ULQ QC diluted 5-fold and 10-fold
Selectivity	No significant interference observed in the 10 blank matrix lots screened.

* Dilution integrity corresponds to dilution linearity

Transferrin-Bound Iron (TBI)

Information Requested	Data
Bioanalytical method validation report location	TAS-V2-753(R3) Validation Report TAS-V2-753(R2) was included as part of the Analytical Report RFR-P5-810(TAS); however, the present table reflects the revised validation report TAS-V2-753(R3). The bioanalytical method and the range did not change. Module 5.3.1.4
Analyte	Transferrin-Bound Iron from Iron Sucrose
Internal standard (IS)	NA
Method description	(b)(4)
Limit of quantitation	50.0 µg/dL
Average recovery of drug (%)	66.2 (CV=6.6%) LOQ: 72.1% (CV = 8.2%) QC1: 66.0% (CV = 3.3%) QC2: 64.6% (CV = 3.7%) QC3: 65.0% (CV = 3.6%) ULQ: 64.0% (CV = 3.8%)
Average recovery of IS (%)	NA (No Internal standard was used.)
Standard curve concentrations (µg/dL)	50.0 µg/dL to 800.0 µg/dL
QC concentrations (µg/dL)	Proxy: 25.0, 50.0 µg/dL, 150.0 µg/dL, 350.0 µg/dL, 500.0 µg/dL, 800.0 µg/dL Human Serum: 50.0, 207.7, 406.6, 555.7, 853.9 µg/dL Human Serum: 205.8, 405.1, 557.9 µg/dL Human Serum: 50.0, 219.3, 417.9, 566.9, 864.8 µg/dL
QC Intraday precision range (%)	Proxy 0.3 % to 3.0%; Human Serum 2.3 % to 6.3 %
QC Intraday accuracy range (%)	Proxy 99.1 % to 102.8 %; Human Serum 86.5 % to 93.9 %
QC Interday precision range (%)	Proxy NA; Human Serum 4.2 % to 9.4 %
QC Interday accuracy range (%)	Proxy NA; Human Serum 89.3 % to 101.0 %
Bench-top stability (hrs)	Proxy 26.0 hours at 22°C Nominal Human Serum 26.4 hours at 22°C Nominal Human Serum containing Iron Sucrose (3500.0 µg/dL) 6.1 hours at 22°C Nominal
Stock stability (days)	Iron Stock Stability: as per certificate of analysis Holo-Transferrin Human Stability: as per certificate of analysis Iron Intermediate solutions & TBI Stock solutions: prepared fresh daily
Processed stability (hrs)	Chromophore stability information is proprietary will be share directly to HA
Freeze-thaw stability (cycles)	Human Serum 5 cycles

	Human Serum containing Iron Sucrose (3500.0 µg/dL), 3 cycles
Long-term storage stability (days)	Proxy 211 days at -20ºC Nominal Human Serum 109 days at -20ºC Nominal Human Serum containing Iron Sucrose (3500.0 µg/dL) 50 days at -20ºC Nominal
Dilution integrity*	Concentration 1.5X ULQ QC diluted 3-fold
Selectivity	No significant interference observed in the 10 blank matrix lots screened.

* Dilution integrity corresponds to dilution linearity.

SOP for bioanalytical method validation submitted?	☒ Yes ☐ No
Is the same anticoagulant used in the pre-method validation study and BE sample analysis? **If not, was cross validation study conducted?**	☒ Yes (K_2EDTA) ☐ No
Does the duration of the each of the LTSS stability parameters support the sample preparation/assay duration and clinical study sample storage temperature?	☒ Yes ☐ No
Was the % recovery consistent across QC concentrations?	☒ Yes (only for TBI assay, no extraction involved and no recovery for TI assay) ☐ No
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	☒ Yes ☐ No

(b)(4)

(b)(4)

(b)(4)

SOP for bioanalytical method validation submitted?	☐ Yes ☒ No
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	☒ Yes ☐ No

Comments on the Pre-Study Method Validation: Inadequate

- Iron is an endogenous compound with a measurable level in human serum (mostly transferrin-bound and an insignificant amount from free or non-transferrin bound iron), the serum iron reference range is 55 – 160 µg/dL in men and 40 – 155 µg/dL in women[21].

- Per the recommendation of current product specific guidance (PSG)[22], the applicant is recommended to measure the total iron (TI) and transferrin-bound iron (TBI) in serum. The BE is based on 90% confidence interval of maximum value of the difference in concentration between TI and TBI over all time points measured, and the difference in AUC between TI and TBI. There is no need to perform baseline correction of total iron and transferrin-bound iron.

Total Iron (TI)

- In current ANDA, the applicant used a (b)(4)

(b)(4)

[21] http://emedicine.medscape.com/article/2085704-overview.
[22] https://www.accessdata.fda.gov/drugsatfda_docs/psg/Iron_sucrose_inj_21135_RV11-13.pdf
[23] GDRP, ANDA 212340, 8/28/2019, Module 5.3.1.4, Appendix 3, Validation Report

(b)(4)

(b)(4)

- The pre-study method validation for TI is **adequate.**

Transferrin-Bound Iron (TBI)

- The applicant used (b)(4)
- (b)(4)

(b)(4)

[30] https://www.fda.gov/files/drugs/published/Bioanalytical-Method-Validation-Guidance-for-Industry.pdf
[31] https://www.fda.gov/media/128343/download

(b)(4)

- (b)(4)

- The pre-study method validation for TBI is **adequate**.

***In vitro* BE study**

- Per draft product specific BE guidance for Iron Sucrose Injection[34], the applicant needs to conduct *in vitro* particle size distribution (PSD) test on at least three lots of both test and reference products. The measured parameters are D_{10}, D_{50}, and D_{90}, and the BE is based on D_{50} and Span [i.e. $(D_{90}-D_{10})/D_{50}$] or polydispersity index using the population bioequivalence statistical approach.

- In the current application, the applicant used a dynamic light scattering method to determine the particle size distribution of test and reference products. Parameters including D_{10}, D_{50}, D_{90}, Span ($D_{90}-D_{10/50}$), Z average, and polydispersity index of dynamic light scattering measurement were recorded. Parameters D_{50} and Span or polydispersity index were evaluated using the population bioequivalence (PBE) statistical approach. However, the applicant did not submit SOP for method validation of PSD study. The applicant will be asked to submit this information.

- Per the applicant submitted validation report (No. IRSUS_AMV_REP_DP_DLS_V01) for size distribution-dynamic light scattering, the applicant using Iron Sucrose Injection (Lot #IRSUS/25, test product, 2017 demo batch) instead of the reference product in the method validation of PSD test. The applicant also used this batch in the PSD study (see product information in Section 4.1.2.1.1.2). This batch of test product was manufactured using API lot #R70197, which is different from bio-lot No. 801859 (API lot #R70196). Since the test product is not an approved drug product at the time of submission, the assessor deems it is more appropriate to use the reference product in method validations of drug product performance. The applicant will be asked to use reference product in its method validation.

- The applicant validated the dilution integrity, assay precision and robustness of the method. The validation results meet acceptance criteria. Based on firm's measurement, the D_{10}, D_{50} and D_{90} for the test product are listed as below.

[34] https://www.accessdata.fda.gov/drugsatfda_docs/psg/Iron_sucrose_inj_21135_RV11-13.pdf

- As a result, the applicant's method validation for PSD testing is **inadequate** per above comments.

3.5 In Vivo Studies

Summary of all Bioequivalence Studies

Pivotal Fasting Study (No. RFR-P5-709)

Total Iron

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: Mean (Range)	Mean Parameters (%CV)						Study Report Location
					Cmax [a] (µg/dL)	Tmax [ab] (hr)	AUC0-t [a] (µg•h/dL)	AUC∞ [c] (µg•h/dL)	T½ [c] (hr)	Kel [c] (hr-1)	
RFR-P5-709	Single Dose Randomized Parallel Design Fasting Bioequivalence Study of Iron Sucrose 100 mg/5 mL Intravenous Injection in Healthy Male and Female Volunteers	Randomized single-dose parallel	**Test:** Iron sucrose Injection USP, 100 mg (5 mL) intravenous injection i.v.; Lot: [801859] **Reference:** Venofer® (iron sucrose),100 mg (5 mL) intravenous injection i.v. Lot [7319A]	200 completing (102/98) Healthy subjects 34 (18-50)	2421.7 (16.6) 2700.6 (17.2)	0.17 (0.17-0.33) 0.17 (0.08-0.50)	12258.1 (17.0) 12990.9 (17.7)	13740.3 (15.5) 14538.8 (17.7)	11.06 (27.6) 11.26 (28.9)	0.0676 (29.3) 0.0657 (23.6)	5.3.1.2

a n= 100 for the Test and the Reference (RFR-P5-709)
b Median (range) is presented. c n= 96 for the Test and n= 97 the Reference (RFR-P5-709);

Transferrin-Bound Iron

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: Mean (Range)	Mean Parameters (%CV)						Study Report Location
					Cmax [a] (µg/dL)	Tmax [ab] (hr)	AUC0-t [a] (µg•h/dL)	AUC∞ [c] (µg•h/dL)	T½ [c] (hr)	Kel [c] (hr-1)	
RFR-P5-709	Single Dose Randomized Parallel Design Fasting Bioequivalence Study of Iron Sucrose 100 mg/5 mL Intravenous Injection in Healthy Male and Female Volunteers	Randomized single-dose parallel, Fasted	**Test:** Iron sucrose Injection USP, 100 mg (5 mL) injection, intravenous i.v.; Lot: 801859 **Reference:** Venofer® (iron sucrose),100 mg (5 mL)intravenous injection i.v. Lot [7319A]	200 completing (102/98) Healthy subjects 34 (18-50)	298.5 (13.7) 292.2 (14.7)	6.08 (0.17-14.00) 6.00 (0.17-16.00)	6482.8 (20.8) 6406.8 (24.4)	7494.8 (17.2) 7503.5 (23.3)	9.75 (32.0) 9.87 (33.4)	0.0776 (29.0) 0.0777 (32.0)	5.3.1.2

a n= 100 for the Test and the Reference (RFR-P5-709); b Median (range) is presented.; c n= 99 for the Test and the Reference

Maximum concentration value and AUC of the Difference between Total Iron and Transferrin-Bound Iron

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: Mean (Range)	Mean Parameters (%CV)			Study Report Location
					Maximum value of the difference in concentration between TI and TBI [a] (µg/dL)	Difference in AUC0-T between TI and TBI [a] (µg•h/dL)	Difference in AUC0-∞ between TI and TBI [b] (µg•h/dL)	
Pivotal BE Study RFR-P5-709	Single Dose Randomized Parallel Design Fasting Bioequivalence Study of Iron Sucrose 100 mg/5 mL Intravenous Injection in Healthy Male and Female Volunteers	Randomized single-dose parallel	**Test:** Iron sucrose Injection USP, 100 mg (5 mL), i.v. inj.; Lot: [801859] **Reference:** Venofer® (iron sucrose),100 mg (5 mL) i.v. Inj. Lot [7319A]	194 completing (101/93) Healthy subjects 34 (18-50)	2227.4 (17.5) 2526.2 (18.2)	5775.3 (22.4) 6598.1 (20.9)	6204.6 (24.3) 7054.8 (21.8)	5.3.1.2

a n= 100 for the Test and n= 94 the Reference for pivotal study
b n= 96 for the Test and n= 90 for the Reference for pivotal study

3.6 OSIS Status

In Vivo PK Study

The clinical study of current application was conducted at Algorithme Pharma Inc. (1200 Beaumont Ave., Mount-Royal, Quebec, Canada H3P 3P1). The sample analysis of current application was performed at Algorithme Pharma Inc. (575 Armand-Frappier Blvd.Laval, Quebec, Canada, H7V 4B3).

Clinical Site

Per GDRP[35] , OSIS recommends accepting data without on-site inspections for the clinical site. The OSIS recently inspected the clinical site and the inspection outcome was "NAI" (No Action Indicated). In addition, the studies submitted in the current ANDA do not indicate any conduct issues and no data integrity deficiencies were identified by the assessor.

Analytical Site

Per the EIR, the inspection at analytical sites is classified as NAI[36]. In addition, the study submitted in the current ANDA does not indicate any conduct issues and no data integrity deficiencies were identified by the assessor.

As a result, the OSIS inspection status of the clinical and analytical sites for the *in vivo* BE study of the current ANDA is considered **complete** at this time.

In Vitro BE Study

The *in vitro* BE (particle size distribution) study of current application was conducted at

(b)(4)

Per GDRP[37], the inspection outcomes were still pending at the time of review completion. The OSIS inspection status of the analytical site for the *in vitro* BE study of the current ANDA is still pending at this time.

[35] GDRP, ANDA 212340-Orig-1, Clinical PK/PD Sites, Site: Algorithme Pharma Inc, Document name: Decline to Inspect_NAI Memo_212340_Alta Sciences_Clinical.pdf, 10/1/2019

[36] (b)(4)

(b)(4)

[37] GDRP, ANDA 212340-Orig-1, In vitro BE sites, Site: RAFARM S.A

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

4.1.1.1.1 Study Information

<table>
<tr><td>Study Number</td><td>RFR-P5-709(TTS) (TI)
RFR-P5-709(TAS) (TBI)</td></tr>
<tr><td>Study Title</td><td>Single Dose Randomized Parallel Design Fasting Bioequivalence Study of Iron Sucrose 100 mg/5 mL Intravenous Injection in Healthy Male and Female Volunteers</td></tr>
<tr><td>Clinical Site
(Name & Address)</td><td>Algorithme Pharma
1200 Beaumont Ave.
Mount-Royal, Quebec, Canada
H3P 3P1</td></tr>
<tr><td>Principal Clinical Investigator</td><td>Eric Sicard, MD.</td></tr>
<tr><td>Dosing Dates</td><td>
<table>
<tr><th>Group*</th><th>Subjects</th><th>Dosing Date</th></tr>
<tr><td>Group A
Group B
Group C
Group D
Group E
Group F
Group G
Group I
Group J
Group K
Group L
Group M
Group N
Group O</td><td colspan="2">(b)(6)</td></tr>
</table>
* Group H was cancelled
</td></tr>
<tr><td>Analytical Site
(Name & Address)</td><td>(b)(4)</td></tr>
<tr><td>Analysis Dates</td><td>2018/8/22 – 2018/11/06</td></tr>
<tr><td>Principal Analytical Investigator</td><td>(b)(4)</td></tr>
<tr><td>Sample Storage :
(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)

(b) Temperature Range (e.g., -20°C to -80°C)</td><td>a) 43 days (TI), 44 days (TBI)

b) -20°C nominal (-10°C to -30°C)</td></tr>
</table>

Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	**Analyte: Total Serum Iron from Iron Sucrose** 146 days at -20°C nominal **Analyte: Transferrin-Bound Iron from Iron Sucrose** 109 days at -20°C nominal in absence of Iron Sucrose, 50 days at -20°C nominal in presence of Iron Sucrose (3500.0 µg/dL), and 128 days at -20°C nominal in presence of Iron Sucrose (2500.0 µg/dL)

4.1.1.1.2 Product (Bio-batch) Information

Product	Test	RLD
Treatment ID	A	B
Product Name	Iron sucrose	Venofer® (iron sucrose)
Manufacturer	Rafarm S.A., Greece	American Regent Inc, USA., Under license from Vifor (International) Inc., Switzerland
Batch/Lot No.	801859	7319A
Manufacture Date	06/01/2018	
Expiration Date		OCT 19
Strength	100 mg/5 mL (5 mL/vial)	5 ml, 20 mg/mL (100 mg/5 mL)
Dosage Form	Solution	Solution
Bio-Batch Size	(b)(4)	
Production Batch Size		
Potency (Assay)	Iron: 103.1% of label claim Sucrose: 305 mg/mL	Iron: 102.1% of label claim Sucrose: 293 mg/mL
Content Uniformity (expressed as mean)	AV=2.5	
Dose Administered	100 mg (5mL)	100 mg (5mL)
Route of Administration	i.v.	i.v.

N/AV: Not available

Are the test and reference products expired at the time of study? **If Yes, please comment**	☐ Yes ☒ No
Is same bio-batch used in the dissolution and all BE studies? **If No, please comment**	☐ Yes ☐ No ☒ N/A
Is the bio-batch size at least the recommended minimum of 100K or 10% of the production batch (whichever is greater) for oral solid dosage form? **If No, please comment**	☐ Yes ☐ No ☒ N/A

Is difference of the potency values for the Test and RLD within 5%? **If No, please comment**	☒ Yes ☐ No

4.1.1.1.3 Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	**Enrolled**: 202 **Dosed**: 202 **Completed**: 200 **Samples Analyzed**:200 **Statistically Analyzed**: Total Iron: 200 Transferrin Bound Iron: 200 Cmax difference: 194
No. of Sequences	Parallel study design (1 sequence in each arm, Test or Reference)
No. of Periods	1
No. of Treatments	2
No. of Groups	14
Washout Period	N/A. This study is designed as a parallel study.
Randomization	☒ Yes ☐ No
Blood Sampling Times	0.00, 0.08, 0.17, 0.33, 0.50, 0.75, 1.00, 1.50, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 9.00, 10.00, 12.00, 14.00, 16.00, 20.00, 24.00, 30.00, 36.00
IRB Approval	☒ Yes Date: 2018/7/13 ☐ No
Informed Consent	☒ Yes Date: 2018/8/7 ☐ No
Length of Fasting	Overnight for at least 10 hours prior to drug administration
Length of Confinement	From at least 14 hours prior to drug administration until 36 hours following drug administration.
Was the drug product administered per labeling for specialized dosage forms e.g. ODT)?	☒ Yes ☐ No ☐ N/A
Safety Monitoring	☒ Yes ☐ No

Comments on Study Design: Adequate

- Per the draft product specific BE guidance[38], a single-dose, randomized, parallel designed *in vivo* fasting BE study is recommended for Iron Sucrose Injection. The drug products should be administered **undiluted** as a slow intravenous injection dose of 100 mg over 5 minutes.

[38] https://www.accessdata.fda.gov/drugsatfda_docs/psg/Iron_sucrose_inj_21135_RV11-13.pdf

- The fasting study (No. RFR-P5-709) was designed as a parallel study. Per clinical study report, a total of 202 subjects were dosed in **fourteen groups**. All the groups were dosing at the same clinical site, but on different dosing date. In order to ensure adequate hydration of the subjects prior to dosing, a volume of approximately 250 mL of normal saline solution was administered intravenously over the course of approximately 60 minutes prior to dosing. Thereafter, a single dose of the assigned formulation was administered **undiluted** by short IV infusion over 5 minutes via an indwelling catheter, infused at a rate of approximately 20 mg/min. The first subject in each group starting at 09:00 (for all Groups), to one subject per every 5 minutes. Fasting continued for at least 4 hours following drug administration, after which a lunch was served.

- The fasting study design is **adequate**.

4.1.1.2 Clinical Results

4.1.1.2.1 Demographic Profile of Subjects

Study No. RFR-P5-709			
		Treatment Groups	
		Test Product N =100	Reference Product N =100
Age (years)	Mean ± SD	33 ± 9	34 ± 9
	Range	18 - 50	19 - 50
Age Groups	< 18 [n (%)]	0	0
	18 – 40 [n (%)]	77 (77.0)	72 (72.0)
	41 – 64 [n (%)]	23 (23.0)	28 (28.0)
	65 – 75 [n (%)]	0	0
	> 75 [n (%)]	0	0
Sex	Male [n (%)]	51 (51.0)	51 (51.0)
	Female [n (%)]	49 (49.0)	49 (49.0)
Race	White [n (%)]	81 (81.0)	77 (77.0)
	Black [n (%)]	8 (8.0)	15 (15.0)
	Asian [n (%)]	3 (3.0)	7 (7.0)
	American Native or Alaska Native [n (%)]	1 (1.0)	0
	Pacific Islander [n (%)]	0	0
	Others [n (%)]	7 (7.0)	1 (1.0)
Ethnicity	Hispanic/Latino [n (%)]	33 (33.0)	27 (27.0)
	Not Hispanic/Not Latino [n (%)]	67 (67.0)	73 (73.0)
BMI (kg/m^2)	Mean ± SD	25.1 ± 2.7	24.9 ± 3.0
	Range	19.4 - 29.9	18.5 - 29.8
Other Factors		NA	NA

NA: Not applicable

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation? If no, please comment.	☒ Yes ☐ No

4.1.1.2.2 Dropout Information

Study No. RFR-P5-709				
Subject No	**Reason for dropout/replacement**	**Period***	**Replaced?**	**Replaced with**
(b)(6)	Subject withdrew consent due to difficulties with blood draws. Date of discontinuation (b)(6) Treatment received: Test	1	No	NA
	Subject withdrew consent due to difficulties with blood draws. Date of discontinuation: (b)(6) Treatment received: Reference	1	No	NA

NA: Not applicable
* As this study was a parallel design, subjects only participated in one study period.

Are dropouts appropriate? If no, please comment.	☐ Yes ☒ No

4.1.1.2.3 Study Adverse Events

Body System / Adverse Event	**Reported Incidence by Treatment Groups**	
	Fasted Bioequivalence Study No. RFR-P5-709	
	Test N =101	**Reference N =101**
Nervous system disorders [n(%)]	29 (28.7)	30 (29.7)
Dysgeusia [n(%)]	11 (10.9)	13 (12.9)
Headache [n(%)]	9 (8.9)	11 (10.9)
Dizziness [n(%)]	4 (4.0)	5 (5.0)
Parosmia [n(%)]	3 (3.0)	3 (3.0)
Somnolence [n(%)]	2 (2.0)	4 (4.0)
Hypoaesthesia [n(%)]	0	2 (2.0)
Sensory Disturbance [n(%)]	2 (2.0)	0
Head Discomfort [n(%)]	1 (1.0)	0
Syncope [n(%)]	1 (1.0)	0
General disorders and administration site conditions [n(%)]	31 (30.7)	24 (23.8)

Injection Site Pain [n(%)]	15 (14.9)	6 (5.9)
Catheter Site Pain [n(%)]	5 (5.0)	2 (2.0)
Injection Site Discomfort [n(%)]	4 (4.0)	1 (1.0)
Catheter Site Bruise [n(%)]	2 (2.0)	2 (2.0)
Infusion Site Pain [n(%)]	3 (3.0)	1 (1.0)
Vessel Puncture Site Bruise [n(%)]	0	4 (4.0)
Fatigue [n(%)]	1 (1.0)	2 (2.0)
Catheter Site Induration [n(%)]	2 (2.0)	0
Catheter Site Related Reaction [n(%)]	1 (1.0)	1 (1.0)
Infusion Site Hypoaesthesia [n(%)]	2 (2.0)	0
Injection Site Hypoaesthesia [n(%)]	1 (1.0)	1 (1.0)
Injection Site Paraesthesia [n(%)]	1 (1.0)	1 (1.0)
Injection Site Warmth [n(%)]	2 (2.0)	0
Vessel Puncture Site Pain [n(%)]	1 (1.0)	1 (1.0)
Catheter Site Hypoaesthesia [n(%)]	1 (1.0)	0
Catheter Site Swelling [n(%)]	1 (1.0)	0
Chills [n(%)]	0	1 (1.0)
Feeling Cold [n(%)]	0	1 (1.0)
Infusion Site Discomfort [n(%)]	0	1 (1.0)
Injection Site Irritation [n(%)]	0	1 (1.0)
Injection Site Reaction [n(%)]	1 (1.0)	0
Injection Site Swelling [n(%)]	1 (1.0)	0
Vessel Puncture Site Induration [n(%)]	0	1 (1.0)
Gastrointestinal disorders [n(%)]	5 (5.0)	5 (5.0)
Nausea [n(%)]	4 (4.0)	3 (3.0)
Dry Mouth [n(%)]	1 (1.0)	1 (1.0)
Diarrhoea [n(%)]	0	1 (1.0)
Vomiting [n(%)]	0	1 (1.0)
Injury, poisoning and procedural complications [n(%)]	4 (4.0)	6 (5.9)
Procedural Dizziness [n(%)]	2 (2.0)	6 (5.9)
Procedural Complication [n(%)]	2 (2.0)	1 (1.0)
Procedural Nausea [n(%)]	1 (1.0)	1 (1.0)
Infusion Related Reaction [n(%)]	1 (1.0)	0
Musculoskeletal and connective tissue disorders [n(%)]	6 (5.9)	2 (2.0)
Pain In Extremity [n(%)]	3 (3.0)	1 (1.0)
Muscle Spasms [n(%)]	2 (2.0)	1 (1.0)
Myalgia [n(%)]	1 (1.0)	0

Eye disorders [n(%)]	2 (2.0)	1 (1.0)
Ocular Hyperaemia [n(%)]	1 (1.0)	0
Photophobia [n(%)]	1 (1.0)	0
Vision Blurred [n(%)]	0	1 (1.0)
Skin and subcutaneous tissue disorders [n(%)]	1 (1.0)	1 (1.0)
Cold Sweat [n(%)]	0	1 (1.0)
Dermatitis Contact [n(%)]	1 (1.0)	0
Cardiac disorders [n(%)]	1 (1.0)	0
Palpitations [n(%)]	1 (1.0)	0
Investigations [n(%)]	0	1 (1.0)
Neutrophil Count Increased [n(%)]	0	1 (1.0)
Psychiatric disorders [n(%)]	1 (1.0)	0
Anxiety [n(%)]	1 (1.0)	0
Reproductive system and breast disorders [n(%)]	0	1 (1.0)
Menstruation Irregular [n(%)]	0	1 (1.0)
Respiratory, thoracic and mediastinal disorders [n(%)]	1 (1.0)	0
Dry Throat [n(%)]	1 (1.0)	0
Total [n(%)]	54 (53.5)	50 (49.5)
Note: Each adverse event is counted only once for each subject within each System Organ Class and MedDRA Preferred Term.		

Subjects Experiencing Emesis (Include in eCTD)

Subject Number	Test/ Reference	Period	Time and Date of dosing	Time and Date of emesis	Duration Between Dosing and Start of Emesis (hours)
[redacted]	Reference	1	9:05	22.23	13.3

Were subjects who experienced vomiting included in statistical analysis?	☒ Yes ☐ No ☐ N/A
If yes, does the time of emesis exceed two times the median Tmax value (immediate release products) or the labeled dosing interval (modified release products)? Please comment.	☐ Yes ☐ No ☒ N/A (Note: It is an IV drug.)
Was the adverse event profile observed comparable for the test and reference product?	☒ Yes ☐ No
Are there any serious adverse events or death?	☐ Yes ☒ No (see comments below)
If yes, then if the study conducted in US, are they reported to the OGD Safety Committee?	☐ Yes ☐ No ☒ N/A

Are there any other safety concerns based on the adverse event profile?	☐ Yes ☒ No (see comments below)

4.1.1.2.4 Protocol Deviations

Study No. RFR-P5-709		
Type	**Subjects # (Test)**	**Subjects # (Ref.)**
Blood sampling time deviations	(b)(6)	
Blood sampling not done		
Extra blood sample collected		
Identification card not given at departure		
Medication restriction not followed		
Samples not stored as required		
Health status questionnaire not performed as required prior to departure		
Xanthine restriction not followed		
Clinic confinement not followed		
Screening: time of repeat assessment not documented		

NA: Not applicable

If the firm used nominal time points, the sampling time deviations (if any) > 5% and 90% CI of any PK parameters is border line, please reanalyze data using actual sampling time	☒ Actual ☐ Nominal

Is the dropout/withdrawal/exclusion of subjects and protocol deviations as per the criteria mentioned in the IRB approved study protocol?	☒ Yes ☐ No

Comments on Clinical Results: Adequate

- There were two (2) subjects withdrawn from the study.
  - Subject No. [-] withdrew consent from the study due to difficulties with blood draws. Per applicant's clinical report, subject No. [-] experienced procedural nausea, catheter site pallor, blurred vision, and procedural dizziness due to catheter insertion before dosing. After dosing with test product, subject No. [-] experienced dizziness, palpitation (feels heart pounding during dosing) after receiving test product. The applicant stated that all these AEs are in mild severity.
  - Subject No. [-] was withdrawn from the study due to difficulties with blood draws. Per applicant's clinical report, subject No. [-] experienced procedural nausea during screening following catheter insertion. After receiving reference product, subject No. [-] experienced vessel puncture site pain and injection site discomfort. All these AEs are in mild severity.

  As a result, the firm's handling of subject dropout is acceptable.

  Adverse Events

- Per applicant's clinical report, one hundred and ten (110) subjects (55%) reported a total of 194 AEs over the course of the study. Of these events, 31 were pre-treatment and the remaining 163 AEs were experienced by one hundred and four (104) subjects (52%). These numbers were different from the applicant provided adverse events summary table in Module 2.7.4 "Summary of Clinical Safety", where the total numbers of adverse events were reported as 104. The assessor deems the applicant only report the percentage not the number of adverse events in the summary table (see table above). For example, the total number of adverse events in the test group is not 54, but 54%.

Table 18 Overview of Adverse Events

Parameter	Test (N=101)	RLD (N=101)	Overall (N=202)
AEs reported [n]	103	91	194
Subjects with at least one AE [n (%)][1]	54 (54)	50 (50)	104 (52)
Subjects with at least one drug-related AE [n (%)][1] [3]	51 (51)	44 (44)	95 (47)
AEs relationship [2]			
Related [n(%)][3]	86 (84)	69 (76)	155 (80)
Not Related [n(%)]	17 (17)	22 (24)	39 (20)
AEs by Onset severity/intensity [2]			
Mild [n(%)]	95 (92)	83 (91)	178 (92)
Moderate [n(%)]	6 (6)	8 (9)	14 (7)
Severe [n(%)]	2 (2)	0	2 (1)
AEs by Maximal Severity/Intensity [2]			
Mild [n(%)]	92 (89)	82 (90)	174 (90)
Moderate [n(%)]	9 (9)	9 (10)	18 (9)
Severe [n(%)]	2 (2)	0	2 (1)
SAEs reported [n] [2]	0	0	0
Subjects with at least one SAE [n (%)][1]	0	0	0
Subjects with at least one drug-related SAE [n (%)][1] [3]	0	0	0
Deaths [n (%)][1]	0	0	0

AEs: Adverse events; SAEs: Serious Adverse Events
N = number of subjects who received a specific treatment
[1] Percentages are based on the number of subjects in the safety population in each treatment group.
[2] Percentages are based on the total number of AEs reported in each treatment group.
[3]Drug-related AE was reported as: Suspected.
Source: Table 14.3.1.1

- Based on the applicant's statement in clinical report, the incidence of AEs was similar for subjects dosed with the Test formulation and the RLD product (54% and 50%, respectively). Drug-related AEs were also reported with a similar incidence for subjects dosed with the Test formulation and the RLD product (51% and 44%, respectively).

- The AEs experienced during the study were deemed mild (174/194; 90%), moderate (18/194; 9%), and severe (2/194; 1%) in intensity. Two subjects (1%) experienced a severe AE during the study: fainting due to venipuncture was experienced following administration of the Test, considered as not related to drug administration and was resolved at the end of the study; and fainting (syncope) was experienced following the administration of the Test product, considered related to drug administration and was resolved at the end of the study. No SAEs and no deaths were reported in any of the subjects dosed in this study. No subject was withdrawn by the investigator due to an AE (safety reason).

- Due to concern to the adverse event (syncope) after receiving test product, and the fainting after catheter insertion, DBIII sent a consult to Division of Clinical Review for the following two questions[39]:

    1) Is the fainting of Subject No. (b)(6) related to the test drug treatment and does it indicate any safety concern for the test product?
    2) Is there any additional information that DBIII needs to communicate to the applicant concerning the fainting after catheter insertion?

- Based on consult response from the DCR[40], the noted two adverse events of fainting were more likely due to vaso-vagal syncope which is commonly seen in a younger population, due to many triggers, including catheter insertion. Hence it does not indicate any safety or quality concern (please see detail discussion in DCR consult attached in Section 4.3.2).

- Subject No. - vomited after 13.3 hours following administration of the reference product. The reviewer deems that the AE of vomiting should not impact the study outcome since the study drug is administered via intravenous route.

- There were ten (10) types of protocol deviations (see Section 4.1.1.2.4). The potential impact of protocol deviations were discussed as follows:

    - There were blood sampling time deviations. The applicant used actual sampling times for time deviations equal to or greater than 2 minutes in PK analysis.
    - There were missing blood samples in nine subjects treated with reference products due to difficulty veins. Per study protocol[41], subjects who do not complete the sampling schedule may be included in the statistical and pharmacokinetic analysis and bioequivalence determination for only the PK parameters that are judged not to be affected by the missing samples. In the case where concentrations of TI and/or TBI cannot be determined due to bioanalytical or clinical reasons, these values will be set to missing for the statistical and pharmacokinetic analysis. The assessor verified that the applicant set these data points to missing in provided SAS dataset.

    There are medication restriction deviations not followed in two subjects treated with reference product, and five subjects treated with test product. Per study protocol, subjects were abstained from taking any OTC products for 7 days prior to dosing and during the study. However, subject No. - took 2 x 500 mg acetaminophen on (b)(6) subject No. - took 2x325 mg acetaminophen on (b)(6) subject No. - took 1X 325/10/5/2mg Acetaminophen/Dextrometorphan HBr/Phenylephrine HCl/Chlorpheniramine maleate on (b)(6); subject No. - took 2 x 500 mg acetaminophen on (b)(6); subject No. - took 2x500 mg Acetaminophen on (b)(6) subject No. - took 2x500 mg Acetaminophen on (b)(6) subject No. - took 2x500 mg Acetaminophen on (b)(6). In study validation,

[39] GDRP, ANDA 212340-ORIG-1, Bioequivalence IR and Consults, Yun Wang (4), 11/13/2019
[40] GDRP, ANDA 212340-Bioequivalence IR and Consults, Respond to Consult Request, 1/29/2020
[41] EDR, ANDA 212340-ORIG-1, 8/28/2019, Module 5.3.1, Section 16.1.1 Protocol and Amendment

the applicant has validated the interference of these compounds to iron assay except for phenylephrine taken by subject No. [redacted] Subject No. [redacted] was dosed on [redacted] thus the medication was taken about six days prior to the dose. Phenylephrine is readily metabolized in GI tract once taken via oral route[42]. The assessor deems the drug will be eliminated by the time of dosing and will not significantly impact the iron assay. These subjects were included in the PK calculation.

- There is xanthine restriction not followed for subject Nos. [redacted]. Per study protocol, subjects should avoid food or beverages containing xanthine for 58 hours prior to each dosing and during study. These three subjects took coffee or chocolate which contains caffeine. The applicant has validated the interference for caffeine in prestudy validation. These subjects were included in the study.
- There are sample storage deviations. Per study protocol, blood samples were to be stored within 90 minutes of collection. The assessor verified that the deviated samples were stored from 93 minutes – 100 minutes. In pre-study validation, bench top stability is established at 25.8 hours for TI assay, and 26.4 hours for TBI assay. Thus, the assessor deems these deviations will not significantly impact the BE outcome.
- Overall, the assessor considers these deviations in Section 4.1.1.2.4 do not have impact on the BE study outcome.

- The applicant's handling of adverse events, dropouts and protocol deviations are **adequate.**

4.1.1.3 Bioanalytical Results

4.1.1.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

SOP No.	Effective Date of SOP	SOP Title
(b)(4)		Sample Coding and Re-assay
		Determination of Total Serum Iron from Iron Sucrose in Human Serum by a Spectrophotometric Method (LOQ 50.0 µg/dL, ULQ 2500.0 µg/dL)
		Determination of Transferrin-bound Iron from Iron Sucrose in Human Serum by a Spectrophotometric Method (LOQ 50.0 µg/dL, ULQ 800.0 µg/dL)
		Sample Analysis for Ligand Binding Assays
		Data Status, Laboratory Investigations and Events
		Calibration Curve Preparation and Acceptance Criteria in Ligand Binding Assays
		Testing of Endogenous Compounds in Ligand Binding Assays

[42] https://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph.aspx?cpnum=3471&sec=monphar&t=0

(b)(4)		Validation of a Bioanalytical Method in Large Molecule Bioanalysis
		Operation and Use of Gen5 Secure Software and BioTek Synergy H4 Hybrid Multi-Mode Microplate Readers
		Incurred Sample Reproducibility

All necessary SOPs submitted?	☒ Yes ☐ No

4.1.1.3.2 Sample Analysis Calibration and Quality Control

Total Serum Iron (TI)

RFR-P5-709(TTS) Total Serum Iron from Iron Sucrose								
Parameter	**Standard Curve Samples**							
Concentration (µg/dL)	50.0	100.0	200.0	400.0	800.0	1600.0	2000.0	2500.0
Inter day Precision (%CV)	3.0	4.3	4.1	4.5	3.9	3.7	4.0	4.3
Inter day Accuracy (%Actual)	99.7	101.6	99.4	99.8	101.1	101.0	100.9	99.2
Linearity	0.97146 – 0.99997							
Linearity Range (µg/dL)	50.0-2500.0							
Sensitivity/LOQ (µg/dL)	50.0							
Parameter	**Quality Control Samples**							
Concentration (µg/dL)	220.2		569.7		1869.8		1019.1	
Inter day Precision (%CV)	5.2		4.3		4.5		4.4	
Inter day Accuracy (%Actual)	98.1		100.5		101.2		100.4	

Transferrin-Bound Iron (TBI)

RFR-P5-709 (TAS) Transferrin-Bound Iron from Iron Sucrose								
Parameter	**Standard Curve Samples**							
Concentration (µg/dL)	25.0	50.0	100.0	200.0	400.0	600.0	800.0	1200.0
Inter day Precision (%CV)	3.6	4.4	4.4	4.3	3.9	4.6	4.6	5.4
Inter day Accuracy (%Actual)	100.4	100.0	100.1	100.5	101.2	98.7	101.3	101.3
Linearity	0.88670 to 0.99989							
Linearity Range (µg/dL)	50.0-800.0							
Sensitivity/LOQ (µg/dL)	50.0							
Parameter	**Quality Control Samples**							
Concentration (µg/dL)	219.3			417.9			566.9	
Inter day Precision (%CV)	6.8			5.5			4.8	
Inter day Accuracy (%Actual)	92.1			92.1			92.4	

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes ☐ No
Are there any concerns related to sample analysis (including rejected runs, reinjection, sample dilution, etc.)? If yes, comment below or consult TL/tertiary reviewer for additional actions	☐ Yes ☒ No
Were 20% of absorbance data included?	☒ Yes ☐ No
Were absorbance data serially or randomly selected?	☒ serially ☐ randomly ☐ N/A
Any interfering peaks in chromatogram?	☐ Yes ☐ No ☒ N/A (Note: It is a spectrophotometric assay.)
Were the absorbance data submitted by the firm acceptable?	☒ Yes ☐ No ☐ N/A
Were 100% raw analytical data, including failed runs, provided?	☒ Yes ☐ No

4.1.1.3.3 Reanalysis of Study Samples

Total Serum Iron (TI)

RFR-P5-709(TTS) Additional information in Module 5.3.1.4								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0	0	0.0	0.0	0	0	0.0	0.0
Reason UCV	106	99	2.1	2.0	102[2]	97[3]	2.0	1.9
Reason >ULQ	80	150	1.6	3.0	80	150	1.6	3.0
Reason CR	4	2	0.1	0.0	4	2	0.1	0.0
Rejected bioanalytical batches[1]	92	201	1.8	4.0	92	201	1.8	4.0
Not evaluable bioanalytical batches[1]	66	70	1.3	1.4	66	70	1.3	1.4
Total	348	522	7.0	10.5	344	520	6.9	10.4

UCV = Unacceptable % C.V. >ULQ = Above the Upper Limit of Quantitation, CR = Outside Truncated Curve Range
1 - Excluding samples also re-assayed with individual repeat codes., 2- Samples [redacted] were not reportable (NR).
3- Samples [redacted] were not reportable (NR).

Transferrin-Bound Iron (TBI)

RFR-P5-709(TAS) Additional information in Module 5.3.1.4								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.0	0.0	0	0	0.0	0.0
Reason UCV	28	25	0.6	0.5	28	25	0.6	0.5
Reason SLP	2	3	0.0	0.1	2	3	0.0	0.1
Reason CR	3	9	0.1	0.2	3	9	0.1	0.2
Rejected bioanalytical batches[1]	175	293	3.5	5.9	175	293	3.5	5.9
Not evaluable bioanalytical batches[1]	75	145	1.5	2.9	75	145	1.5	2.9
Total	283	475	5.7	9.5	283	475	5.7	9.5

UCV = Unacceptable % C.V. SLP = Sample Lost in Processing, CR = Outside Truncated Curve Range, 1 - Excluding samples also re-assayed with individual repeat codes.

Does the reviewer agree with the reanalysis of study samples: analytical and/or PK repeat?	☐ Yes ☒ No (refer to deficiency in the Deficiency Letter)
If no, is recalculation of PK parameters necessary?	☐ Yes ☒ No ☐ N/A
Did recalculation of PK parameters change the study outcome?	☐ Yes ☒ No ☐ N/A
Are the PK parameters of reanalysis still within the acceptance limits for the 90% CI?	☐ Yes ☐ No ☒ N/A

Comments on Bioanalytical Results: Inadequate

Total Serum Iron (TI)

- Iron Sucrose (Venofer®) was (b)(4) (b)(4) The QC and CC sample preparation are the same as the ones in pre-study validation.

- The applicant used 311 (6.2%) of total 4990 study samples for incurred sample reanalysis (ISR) of TI. The ISR sample size meets the "10% reanalysis of the first

1000 samples and 5% reanalysis of the remaining samples" per Bioanalytical Method Validation Guidance[43]. The ISR testing was performed as per SOP (b)(4) (Incurred Sample Reproducibility; effective date: (b)(4) (b)(4) (b)(4)" per the SOP, which was in accordance to the criteria for ligand binding assay per Guidance for Industry: Bioanalytical Method Validation (May 2018). The current bioanalytical method validation guidance did not clearly define the (b)(4)

(b)(4)

Therefore, the ISR testing is acceptable, indicating that the TI method is reproducible.

(b)(4)

- **Repeat Analysis for TI**

1. In the fasting study, a total of 870 samples (17.4%) were reanalyzed out of 4990 study samples for TI.

2. Two hundred and five (205) samples (106 for the test and 99 for the reference) were reanalyzed under the reason of "Unacceptable %CV (Code UCV)". The SOP # (b)(4) (Sample Coding and Re-assay; effective Date: (b)(4) defines the "UCV" as the following:

   (b)(4)

   The applicant submitted raw absorbance data for these samples. The assessor checked the raw data for the samples coded with this reason. All the reanalysis samples met the criterion in the bioanalytical lab's SOP # (b)(4)

3. Two hundred and thirty (230) samples (80 for test and 150 for the reference) were reanalyzed under the reason of (b)(4). The SOP # (b)(4) defines the "above the upper limit of quantitation". The applicant submitted raw absorbance data for these samples. In prestudy method validation, (b)(4) (b)(4) for the samples coded with this reason. All the reanalysis samples met the criterion in the bioanalytical lab's SOP # (b)(4)

[43] https://www.fda.gov/files/drugs/published/Bioanalytical-Method-Validation-Guidance-for-Industry.pdf
[44] https://www.fda.gov/files/drugs/published/Bioanalytical-Method-Validation-Guidance-for-Industry.pdf
[45] https://www.fda.gov/media/128343/download
[46] EDR, ANDA 212340, 8/28/2019, Module 5.3.1.4, TTS-Validation report, Page 4/87

4. Six (6) samples (4 for the test and 2 for the reference) were reanalyzed under the reason of "CR (outside truncated curve range)". The SOP (b)(4) defines the "CR" as the following. The applicant submitted raw absorbance data for these samples. The assessor checked the raw data for the samples coded with this reason. All the reanalysis samples met the criterion in the bioanalytical lab's SOP (b)(4)

(b)(4)

5. There are 25 samples are repeated in error and not calculated in the number of repeat samples in summary table. The applicant provided the original value (report value) and repeat value comparison table, and the absolute difference are betweer (b)(4) %. The assessor deems the results should not significantly impact the BE study outcome.

6. Batch Rejections:

- All study samples for TI were analyzed in 260 analytical batches including batches for repeats and ISR. The nineteen rejected batches (- %) and rejection reasons are listed as below:

1) Batch No. (b)(6) for subject - The coefficient of determination was (b)(4)
2) Batch No. (b)(6) for subject - (b)(4) % of non-zero calibrants had an accuracy (%Nominal) within (b)(4) %.
3) Batch No. (b)(6) for subject - : (b)(4) % (2/3) of QC samples, including (b)(4) % at each concentration, had a %Nominal within (b)(4) %.
4) Batch No. (b)(6) for subject No. - : (b)(4) % of non-zero calibrants were acceptable.
5) Batch No. (b)(6) for subject No. - : (b)(4) % (2/3) of QC samples, including (b)(4) % at each concentration, had a %Nominal within (b)(4) %.
6) Batch No. (b)(6) for subject No. - : (b)(4) % (2/3) of QC samples had a %Nominal within (b)(4) %.
7) Batch No. (b)(6) for subject No. - : The coefficient of determination was (b)(4)
8) Batch No. (b)(6) for subject No. - (b)(4) % (2/3) of QC samples had a % Nominal within (b)(4) %.
9) Batch No. (b)(6) for subject No. - : (b)(4) % (2/3) of QC samples had a (b)(4) %.

10) Batch No. [redacted] for subject No. [redacted] % (2/3) of QC samples had a % Nominal within [redacted] %.
11) Batch No [redacted] for subject No. [redacted]: The coefficient of determination was [redacted]
12) Batch No. [redacted] for subject No. [redacted]: [redacted] % of non-zero calibrants were acceptable.
13) Batch No. [redacted] for subject No. [redacted]: [redacted] % (2/3) of QC samples had a % Nominal within [redacted] %.
14) Batch No. [redacted] for subject No. [redacted]: [redacted] % (2/3) of QC samples had a % Nominal within [redacted] %.
15) Batch No. [redacted] for subject No. [redacted] [redacted] % (2/3) of QC samples had a % Nominal within [redacted] %.
16) Batch No. [redacted] for subject No. [redacted]: [redacted] % (2/3) of QC samples had a % Nominal within [redacted] %.
17) Batch No. [redacted] for subject No. [redacted]: The coefficient of determination was [redacted]
18) Batch No. [redacted] for subject No. [redacted]: Two consecutive calibrants had an accuracy (%Nominal) outside [redacted] %.
19) Batch No. [redacted] for subject No. [redacted] [redacted] % of QC1 sample concentrations were within [redacted] % of the nominal concentration.

The applicant submitted raw absorbance data for these samples. SOP No. [redacted] (Calibration Curve Preparation and Acceptance Criteria in Ligand Binding Assays) set the batch acceptance criteria. The assessor verified that these batch rejections meet acceptance criteria set in SOP No. [redacted] except for the batches rejected under reason of "The coefficient of determination was [redacted]." The assessor did not find this acceptance criteria in SOP No. [redacted] Another in-house ANDA [redacted] which bioanalytical study conducted at the same site as current ANDA also did not use this criterion as batch rejection[47]. **The applicant will be asked to clarify the SOP that pre-defined this batch acceptance criteria and provide evidence to support why they [redacted] as R^2 cutoff.**

- There are analytical batches categorized as "Not evaluable" and repeated, and the reasons are listed as below. The assessor deems these batches were categorized appropriately.
  1) Batch No. [redacted] for subject No [redacted]: A bioanalytical issue was observed (error occurred during solution preparation: wrong plate used). No original analytical results available.
  2) Batch No. RFR709.23 (TTS) for ISRs-Part 2: A bioanalytical issue was observed (error occurred during solution preparation: incubation time not respected).

47 [redacted]

3) Batch No. RFR709.33 (TTS) for ISRs-Part 2: A bioanalytical issue was observed (error occurred during solution preparation: incubation time not respected).
4) (b)(6) for subject No. - A bioanalytical issue was observed (error occurred during solution preparation: Incubation time not respected).
5) Batch No. (b)(6) for subject No. -: A bioanalytical issue was observed (presence of bubbles in wells).
6) Batch No. (b)(6) for subject No. -: A bioanalytical issue was observed (error occurred during sample preparation: Reading of plate stopped by error. No original analytical results available).
7) Batch No. (b)(6) for subject No. -: A bioanalytical issue was observed (error occurred during solution preparation: Incubation time exceeded).
8) Batch No. (b)(6) for subject No. - A bioanalytical issue was observed (error occurred during solution preparation: Incubation time exceeded).

- Overall, the analysis of fasting study samples for TI is **inadequate** due to the deficiencies listed in the deficiency letter.

Transferrin-Bound Iron (TBI)

- TBI was (b)(4) (b)(4)
- The applicant also included (b)(4) (b)(4) was deemed acceptable[48].
- The applicant used (b)(4) was performed as per SOP (b)(4) (Incurred Sample Reproducibility; effective date: (b)(4) (b)(4)

[48] (b)(4)

Guidance for Industry: Bioanalytical Method Validation (May 2018). A total 295 out of 310 samples [redacted] %) were found to be within [redacted] % difference. The current bioanalytical method validation guidance did not clearly define [redacted] Per M10 draft bioanalytical guidance[50], [redacted]

(b)(4)

[redacted]. Therefore, the ISR testing is acceptable, indicating that the TBI method is reproducible.

(b)(4)

- **Repeat Analysis**

1. In the fasting study, a total of 758 samples (15.2 %) were reanalyzed out of 4990 study samples for TBI.

2. Fifty-three (53) samples (28 for the test and 25 for the reference) were reanalyzed under the reason of "Unacceptable %CV". The SOP [redacted] (Sample Coding and Re-assay; effective Date: [redacted]) defines the "UCV" as the following:

   (b)(4)

   The applicant submitted raw absorbance data for these samples. The assessor checked the raw data for the samples coded with this reason. All the reanalysis samples met the criterion in the bioanalytical lab's SOP #[redacted]

3. Five (5) samples (2 for test and 3 for the reference) were reanalyzed under the reason of "SLP (Sample lost in processing)". The SOP #[redacted] defines the "SLP" as the following. The samples are listed as below. The applicant submitted raw absorbance data for these samples. There are [redacted] % CV difference between the duplicate wells for sample [redacted] (CV% = [redacted]) and [redacted] (one well positive and one well negative absorbance). Overall the assessor deems these repeats should not significantly impact the BE outcome.

   (b)(4) (b)(6)

[49] https://www.fda.gov/files/drugs/published/Bioanalytical-Method-Validation-Guidance-for-Industry.pdf
[50] https://www.fda.gov/media/128343/download

4. Twelve (12) samples (3 for the test and 9 for the reference) were reanalyzed under the reason of "CR (outside truncated curve range)". The SOP [redacted] defines the "CR". The applicant submitted raw absorbance data for these samples. The assessor checked the raw data for the samples coded with this reason. All the reanalysis samples met the criterion in the bioanalytical lab's SOP #[redacted]

(b)(4) (b)(6)

5. Batch Rejections:

➢ All study samples for TBI were analyzed in 252 analytical batches including batches for repeats and ISR. The rejected batches and rejection reasons are listed as below:

1) Batch No. [redacted] for subject [redacted]: The coefficient of determination was [redacted]
2) Batch No. RFR709.22 (TAS) for ISRs-Part 1: The coefficient of determination was [redacted]
3) Batch No. [redacted] for Subject No. [redacted] & Repeats-Part 5: The coefficient of determination was [redacted]
4) Batch No. [redacted] for Subject No. [redacted] The coefficient of determination was [redacted]
5) Batch No. [redacted] for Subject No. [redacted] The coefficient of determination was [redacted]
6) Batch No. [redacted] for Subject No. [redacted]: [redacted]% (2/3) of post-column QC samples had a %Nominal within [redacted]% or a CV [redacted]%.
7) Batch No. [redacted] for Subject No. [redacted] [redacted]% of non-zero calibrants had an accuracy (%Nominal) within [redacted]% (within [redacted]% for the LOQ calibrant).
8) Batch No. [redacted] for Subject No. [redacted]: [redacted]% of non-zero calibrants had an accuracy (%Nominal) within [redacted]% (within [redacted]% for the LOQ calibrant).
9) Batch No. RFR709.98 (TAS) for ISRs-Part 9: [redacted]% (2/3) of post-column QC samples had a %Nominal within [redacted]% or a [redacted]%.
10) Batch No. [redacted] for Subject No. [redacted]: [redacted]% (2/3) of post-column QC samples had a %Nominal within [redacted]% or a [redacted]%.
11) Batch No. R[redacted] for Subject No. [redacted]: [redacted]5% of non-zero calibrants had an accuracy (%Nominal) within [redacted]% (within [redacted]% for the LOQ calibrant).
12) Batch No. [redacted] for Subject No. [redacted] The coefficient of determination was [redacted]
13) Batch No. [redacted] for Subject No. [redacted] [redacted]% of non-zero calibrants had an accuracy (%Nominal) within [redacted]% (within [redacted]% for the LOQ calibrant).

14) Batch No. [redacted] for Subject No. [redacted]: The coefficient of determination was [redacted]
15) Batch No. [redacted] for Subject No. [redacted]: [redacted] non-zero calibrants were acceptable.
16) Batch No. [redacted] for Subject No. [redacted] Repeats-Part 24: The coefficient of determination was [redacted]
17) Batch No. [redacted] for Subject No. [redacted]: The coefficient of determination was [redacted]
18) Batch No. [redacted] for Subject No. [redacted] [redacted]% of the QC samples had a % Nominal within [redacted]%.
19) Batch No. [redacted] for Subject No. [redacted]: The coefficient of determination was [redacted]
20) Batch No. [redacted] for Subject No. [redacted]: [redacted]% of non-zero calibrants had an accuracy (%Nominal) within [redacted]% (within 80.0% to 120.0% for the LOQ calibrant).
21) Batch No. [redacted] for Subject No. [redacted] & Repeats Part 29: The coefficient of determination was [redacted]
22) Batch No. [redacted] for Subject No. [redacted] [redacted]% of non-zero calibrants had an accuracy (%Nominal) within [redacted]% (within [redacted]% for the LOQ calibrant.
23) Batch No. [redacted] for Subject No. [redacted]: [redacted]% (2/3) of post-column QC samples had a %Nominal within [redacted]%.
24) Batch No. [redacted] for Subject No. [redacted]: The coefficient of determination was [redacted]
25) Batch No. [redacted] for Subject No. [redacted]: [redacted]% (2/3) of post-column QC samples had a %Nominal within [redacted]%. (repeat in error)
26) Batch No. RFR709.254 (TAS) for ISRs-Part 14: The coefficient of determination was [redacted]

The applicant submitted raw absorbance data for these samples. SOP No.

(b)(4)

(b)(4)

- There are analytical batches categorized as "Not evaluable" and repeated, and the reasons are listed as below. The assessor deems these batches were categorized appropriately.
  1) Batch No. [redacted] for subject No. [redacted]: A bioanalytical issue was observed (error occurred during solution preparation: incubation time exceeded).
  2) Batch No. [redacted] for subject No. [redacted]: A bioanalytical issue was observed [redacted]
  3) Batch No. [redacted] for subject No. [redacted] Repeats-Part 25: A bioanalytical issue was observed (error occurred during sample preparation: [redacted]. No original analytical results available.).
  4) Batch No. [redacted] for subject No. [redacted]: A bioanalytical issue was observed (error occurred during sample preparation: Wrong QCs used. No original analytical results available).
  5) Batch No. [redacted] for subject No. [redacted] A bioanalytical issue was observed (error occurred during sample preparation: Wrong QCs used. No original analytical results available).
  6) Batch No. [redacted] for subject No. [redacted]: A bioanalytical issue was observed (error occurred during sample preparation: Sample splashed on plate sealer).
  7) Batch No. [redacted] for subject No. [redacted]: A bioanalytical issue was observed (error occurred during sample preparation: Sample splashed on plate sealer).
  8) Batch No. [redacted] for subject No. [redacted] Repeats-Part 29: A bioanalytical issue was observed (error occurred during calibrant aliquoting).
  9) Batch No. [redacted] for subject No. [redacted] A bioanalytical issue was observed (error occurred during sample preparation: different reader used for reading 1 and reading 2).
  10) Batch No. [redacted] for subject No. [redacted]: A bioanalytical issue was observed (error occurred during sample preparation: different reader used for reading 1 and reading 2).

- Overall, the analysis of fasting study samples for TBI is **inadequate** due to the deficiencies listed in the deficiency letter.

4.1.1.4 Pharmacokinetic Results

4.1.1.4.1 Arithmetic Mean Pharmacokinetic Parameters

TI (Assessor Calculated, no baseline correction)

Fasting Bioequivalence Study No. RFR-P5-709									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *µg/dl)	12270.14	16.85	7673.77	18197.21	12992.80	17.66	7899.84	18489.38	0.94
AUC∞ (hr *µg/dl)	13898.71	16.23	8857.65	20303.40	14635.30	17.29	9988.88	23438.53	0.95
Cmax (µg/dl)	2421.72	16.63	1540.00	3625.80	2700.64	17.22	1736.90	4659.90	0.90
Tmax* (hr)	0.17	--	0.17	0.33	0.17	--	0.08	0.50	1.00
Kel (hr^{-1})	0.06	30.42	0.02	0.13	0.06	27.39	0.01	0.10	1.00
T1/2 (hr)	12.40	40.99	5.21	44.16	12.56	47.49	7.11	49.95	0.99

* Tmax values are presented as median, range.

TBI (Assessor Calculated, no baseline correction)

Fasting Bioequivalence Study No. RFR-P5-709									
Parameter (units)	Test				Reference				T/R
	Mean	% CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *µg/dl)	6530.75	19.96	2668.36	9676.66	6478.82	23.02	2665.26	10478.05	1.01
AUC∞ (hr *µg/dl)	7531.15	19.18	3192.69	12032.99	7644.21	24.12	2846.98	14257.53	0.99
Cmax (µg/dl)	298.50	13.70	151.90	404.30	292.22	14.68	188.50	415.60	1.02
Tmax* (hr)	6.00	--	0.17	14.00	6.00	--	0.17	16.00	1
Kel (hr^{-1})	0.07	28.57	0.03	0.12	0.07	28.57	0.01	0.13	1
T1/2 (hr)	10.49	28.79	5.62	22.74	11.30	50.18	5.49	46.22	0.93

* Tmax values are presented as median, range.

TI- TBI (For Cmax calculation)

Fasting Bioequivalence Study No. RFR-P5-709									
Parameter (units)	Test				Reference				T/R
	Mean	% CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *µg/dl)	5616.61	22.50	1633.00	9453.61	6378.38	21.23	4109.63	10001.92	0.88
AUC∞ (hr *µg/dl)	7005.13	52.70	1684.73	30251.31	7400.70	34.32	4187.77	20202.39	0.95
Cmax (µg/dl)	2227.42	17.47	1375.60	3359.50	2515.33	17.99	1593.70	4467.00	0.89
Tmax* (hr)	0.17	--	0.17	0.33	0.17	--	0.08	0.33	1.00
Kel (hr^{-1})	0.05	62.99	0.00	0.15	0.06	62.60	0.00	0.19	0.87
T1/2 (hr)	25.29	174.97	4.54	399.82	22.28	160.85	3.69	270.73	1.14

* Tmax values are presented as median, range.

4.1.1.4.2 Geometric Means and 90% Confidence Intervals - Applicant Calculated

Iron Sucrose USP Injection (No of subjects completed = 200) Dose: 1 x 100 mg Least Squares Geometric Means*, Ratio of Means (%), and 90% Confidence Intervals (%) Pivotal Fasted Bioequivalence Study (Study No.RFR-P5-709)							
Parameter	Test	N	Reference	N	Ratio	90% C.I.	
						Lower	Upper
Difference in AUC0-T	5583.5	100	6453.0	94*	86.53	81.26	92.13
Difference in AUC0-∞	5967.8	96	6886.0	90	86.67	80.97	92.76
Maximal Difference in Concentration	2194.3	100	2485.4	94	88.29	84.63	92.10

*The applicant excluded subjects Nos [redacted] (reference treatments) in PK and statistical calculation for all three PK parameters. The applicant stated that "*Due to the early missing blood samples, subjects [redacted] were included in the TI and TBI PK analysis, but excluded from PK and statistical analysis of the maximum value of the difference in concentration between TI and TBI, and the difference in AUC between TI and TBI*[51]".

In addition, the assessor found the applicant set the following subjects' maximal difference in concentration" value in missing in their SAS dataset: Nos. [redacted].

[51] Page 56/111 of fasting study report

4.1.1.4.3 Geometric Means and 90% Confidence Intervals - Assessor Calculated

Iron Sucrose USP Injection (No of subjects completed = 200) Dose: 1 x 100 mg Least Squares Geometric Means*, Ratio of Means (%), and 90% Confidence Intervals (%)							
Pivotal Fasted Bioequivalence Study (Study No.RFR-P5-709)							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *µg/dl)	5548.15	100	6367.12	100	0.87	81.92	92.68
AUC∞ (hr *µg/dl)	5983.54	85*+	6836.95	82*+	0.88	81.54	93.93
Cmax (µg/dl)	2194.26	100	2476.06	100	0.89	85.04	92.35

+The following subjects are excluded from AUCi calculation due to nonlinear elimination phase or missing samples. **TI**: Test: Subject Nos. [redacted]
TBI: Test: Subject Nos. [redacted]; Ref: Subject Nos. [redacted]

The final subject exclusion will be: **Test (15)**: [redacted]
Ref (18): Subject Nos. [redacted]

4.1.1.4.4 Additional Information for the Study

Root Mean Square Error	AUCt: 0.2639 AUCi: 0.2737 Cmax: 0.1765
Is there a Tmax difference between Test and Reference? **If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference)**	☐ Yes ☒ No
Were the subjects dosed in groups? **If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary?**	☒ Yes ☐ No group*treatment interaction is not significant for all three PK parameters. See table below
Are there measurable drug concentrations at 0 hr? **If yes, please comment (and take necessary action, if needed)**	☒ Yes (endogenous analyte) ☐ No
Are there first measurable drug concentration as Cmax? **If yes, please comment**	☐ Yes ☒ No
Are there Cmax at the first post-dose sampling time point? **If yes, is the study (sample) design adequate?**	☒ Yes ☐ No (Note: IV administration) TI:2, [redacted] See comments below.

TI

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	100	0.88	0.59	0.97
Reference	100	0.89	0.59	0.96
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below	The following subjects has ratio less than 0.8: Test: Subject Nos. [redacted] See comments below.			

TBI

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	100	0.87	0.71	0.95
Reference	100	0.85	0.49	0.95
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below	The following subjects has ratio less than 0.8. Test: Subject Nos. [redacted] Ref: Subject Nos. [redacted]. See comments below.			

Group Analysis Consideration

Is the drug product highly variable drug? If yes, please check the current DB policy to evaluate group effect: \\cdsnas\ogds11\firmsnz\ppd\controls\98-392a.doc	☐ Yes ☒ No

If no, is the group*treatment interaction term statistically significant at alpha=0.1 (i.e., p < 0.1)? If p ≥ 0.1, no need to consider group effect.	No.
	lnAUCt: p=0.5915;
	lnAUCi: p=0.6240;
	lnCmax: p=0.1637

If yes, did you use the statistical model with group effect included?	☐ Yes ☒ No
If yes, specify which PK parameter(s)	N/A
If yes (i.e. group*treatment term is significant), was each group analyzed separately?	☐ Yes ☐ No ☒ N/A
If each group was analyzed, did any individual group meet BE criteria?	☐ Yes ☐ No ☒ N/A
If none of individual group meets the BE criteria, did you have other justifications for accepting the data? If yes, please provide justifications.	☐ Yes ☐ No ☒ N/A

Comments on PK results: Adequate

- The current draft product specific BE guidance for Iron Sucrose Injection recommends measure total iron and transferrin-bound iron concentration in serum. There is no need to perform baseline correction for both analytes. BE is based on the 90% confidence interval of :1) Maximum value of the difference in concentration between Total Iron and Transferrin-bound Iron over all time points measured; and 2) Difference in AUC between Total Iron and Transferrin-bound Iron. AUC should be calculated separately to maximize the number of data points used in cases of missing data[52]. In current ANDA, the applicant used the same method to establish BE as recommended in the guidance.

➢ **TI**

- Per applicant's clinical study report, the terminal phase of TI could not be adequately estimated for 7 subjects:

Table 11 Summary of Non-Evaluable Elimination of Total Iron

Subject	Treatment	Period	Reason*
	RLD	1	C
	RLD	1	B
	Test	1	B
	RLD	1	B
	Test	1	B
	Test	1	C
	Test	1	C

*Reasons:

A. Best-Fit Range (e.g. λ_Z negative, less than 3 data points after C_{max})
B. $R^2 < 80\%$
C. The corresponding terminal half-life value was larger than 2 times the time interval over which λ_Z was estimated (i.e. $T_{half} \leq$ twice the time interval difference between λ_z upper and λ_z lower)
D. No Log Linear Terminal Phase

- Based on the assessor's calculation, the following subjects has AUCt/AUCi ratio less than 0.8 for TI. Test treatment: Subject Nos. (b)(6) Reference treatment: (b)(6). The plasma concentration vs time profile for Subject - (test, Ratio = -) and Subject - (reference, Ratio = -) are listed as below. These subjects will be excluded in AUCi calculation due to nonlinear elimination phase.

[52] https://www.accessdata.fda.gov/drugsatfda_docs/psg/Iron_sucrose_inj_21135_RV11-13.pdf

(b)(4)
(b)(6)

Subject No. [redacted] (reference treatment) had a TI Cmax at the first post-dose sampling point (0.08 hr) of the concentration time curve, and the first data point at 0.00 hour was missing. In addition, subject Nos. [redacted] (reference treatment) has Cmax at the first post-dose sampling point. In addition, Subject No. [redacted] missing samples at 0.08 and 0.17 hours, and the Cmax is at 0.33 hours which is the first available post-dose sample for this subject. Subject Nos. [redacted] missed the 0.08 hour sample, and the Cmax is at 0.17 hours which is the first available post-dose sample for these subjects. In applicant's clinical report[53], "*Three subjects had a Cmax value at the first point of the concentration time curve. Since the planned sampling schedule included early samples and frequent sampling around the predicted Tmax to provide a reliable estimate of peak exposure, study results are considered reliable. The three early maximum values did not interfere with the general appropriateness of the sampling schedule.*" Other in-house ANDA for the same drug product, e.g, ANDA 208977[54], has sampling time point as early as 0.03 hour post-dose. However, in current ANDA, the drug product is administrated via IV infusion over 5 minutes (0.08 hour). Per clinical report (page 28/111), the current 0.08 hour post-dose sampling time is immediately after the end of the slow IV infusion, thus it is practically impossible to have any earlier sampling time point than 0.08 hour. Thus, the applicant's sampling design is adequate. These subjects were still included in the PK and statistical calculation for assessor.

- Based on the applicant provided data, the following subjects missing the 0.00 hour samples: Nos [redacted] (R), [redacted] (T), [redacted] (T), [redacted] (R), [redacted] (T), [redacted] (R). The applicants set these samples as missing. The applicant set the predose concentration as 0 for these concentrations for the difference between TI and TBI in the SAS dataset. The assessor set these samples as missing in the PK and statistical calculation.

- The applicant reported missing data is listed as below. Due to early missing samples, the applicant included subject Nos. [redacted] in the TI and TBI PK analysis but excluded from PK and statistical analysis from the maximum value of the difference of TI-TBI, and the difference in AUC between TI and TBI. The assessor noticed that applicant did not give reason for some of the missing samples in the SAS dataset, especially the missing predose samples as discussed above. In addition, the assessor found the applicant set the following subjects' "maximal difference in concentration" value in "missing" in their SAS dataset: Nos. [redacted], [redacted].

[53] EDR, ANDA 212340, Module 5.3.1.2, Study report, Page 46/111
[54] GDRP, ANDA 208977-ORIG-1-RESUB-5, Bioequivalence Review, Yaning Sun, 1/3/2020

Table 17 Summary of Missing Concentrations

Subject	Formulation	Sampling time (hours)	Code	Analyte
[redacted]	RLD	0.17	NS	TI and TBI
	RLD	0.33	NS	TI and TBI
	RLD	36.00	NR	TI
	Test	36.00	NR	TI
	Test	30.00	NR	TI
	RLD	30.00	NR	TI
	Test	24.00	NR	TI
	RLD	3.00	NS	TI and TBI
	Test	24.00	NR	TI
	RLD	16.00	NS	TI and TBI
	RLD	0.08	NS	TI and TBI
	RLD	0.17	NS	TI and TBI
	RLD	0.33	NS	TI and TBI
	RLD	0.08	NS	TI and TBI
	RLD	0.08	NS	TI and TBI
	RLD	0.08	NS	TI and TBI

NR: Not Reportable; NS: No Sample
Source: Appendix 16.2.6.1.1 and Appendix 16.2.6.2.1

➢ TBI

- Per applicant's clinical study report, the terminal phase of TBI could not be adequately estimated for 2 subjects:

Table 14 Summary of Non-Evaluable Elimination of Transferrin-Bound Iron

Subject	Treatment	Period	Reason*
[redacted]	Test	1	B
	RLD	1	C

*Reasons:
E. Best-Fit Range (e.g. λ_Z negative, less than 3 data points after C_{max})
F. $R^2 < 80\%$
G. The corresponding terminal half-life value was larger than 2 times the time interval over which λ_Z was estimated (i.e. $T_{half} \leq$ twice the time interval difference between T_{LQC} and T_{LIN})
H. No Log Linear Terminal Phase

- Based on the assessor's calculation, the following subjects have AUCt/AUCi ratio less than 0.8 for TBI. Test treatment: Subject Nos. [redacted]; Reference treatment: [redacted] The plasma concentration vs time profile for subject [redacted] (reference, Ratio = 0.49) and subject [redacted] (test, Ratio = 0.71) are listed as below. These subjects will be excluded in AUCi calculation due to nonlinear elimination phase or missing samples.

(b)(4)
(b)(6)

- Based on the applicant provided data, the following subjects missing the 0.00 hour TBI samples: Nos. [redacted] (R), [redacted] (T), [redacted] (T), [redacted] (T), [redacted] (R), [redacted] (R), [redacted] (R), [redacted] (T), [redacted] (T), [redacted] (R), [redacted] (R). The applicants set these samples as missing. The applicant set the pre-dose concentration as 0 for these concentrations for the difference between TI and TBI in the SAS dataset. The assessor set these samples as missing in the PK and statistical calculation.

- Based on the applicant's results, the 90% CIs for test/reference ratios of the least square geometric means of maximum value of difference between TI and TBI and Difference in AUC between TI and TBI meet the BE limits of 80.00- 125.00%.

- The subjects were divided into fourteen (14) groups and dosed at the same clinical site, 2-12 days apart. The applicant stated that they tested group-by-treatment effect at 5% level for all parameters and found not statistically significant. The assessor used SAS GLM procedure to assess the significance of the group*treatment interaction. The statistical model includes "*GRP, TRT, TRT*GRP*". There was no significant group*treatment interaction ($p \geq 0.10$) for AUCt, AUCi, and Cmax (lnAUCt: p=0.5915; lnAUCi: p=0.6240; lnCmax: p=0.1637). Thus, the assessor dropped the group*treatment term in the final statistical model.

➢ **Calculation of maximum value of TI-TBI (both baseline uncorrected)**

The assessor subtracted the TI concentration with TBI concentration for all time points measured for all subjects. All negative values were set to zero (0). Please see subject exclusion in the footnote of Section 4.1.1.4.3 and discussion above. The maximum value of the difference was the Cmax of iron sucrose-associated iron concentration. Based on assessor's calculation, the 90% CIs for test/reference ratios of the least square geometric means of maximum value of difference between TI and TBI meet the BE limits of 80.00-125.00%. There are slightly difference between the applicant and assessor's calculation results due to the assessor used all 200 subjects, but the applicant used 194 subjects in the calculation.

➢ **Calculation of AUC_TI – AUC_TBI (both baseline uncorrected)**

The reviewer first calculated AUCt and AUCi for baseline uncorrected TI and TBI. AUC_TI – AUC_TBI represents the AUC of iron sucrose associated iron. Please see subject exclusion in the footnote of Section 4.1.1.4.3 and discussion above. Based on assessor's calculation, the 90% CIs for test/reference ratios of the least square geometric means of difference in AUC between TI and TBI meet the BE limits of 80.00- 125.00%.

4.1.1.5 Overall Comment

Was the fasting bioequivalence study acceptable? Inadequate.

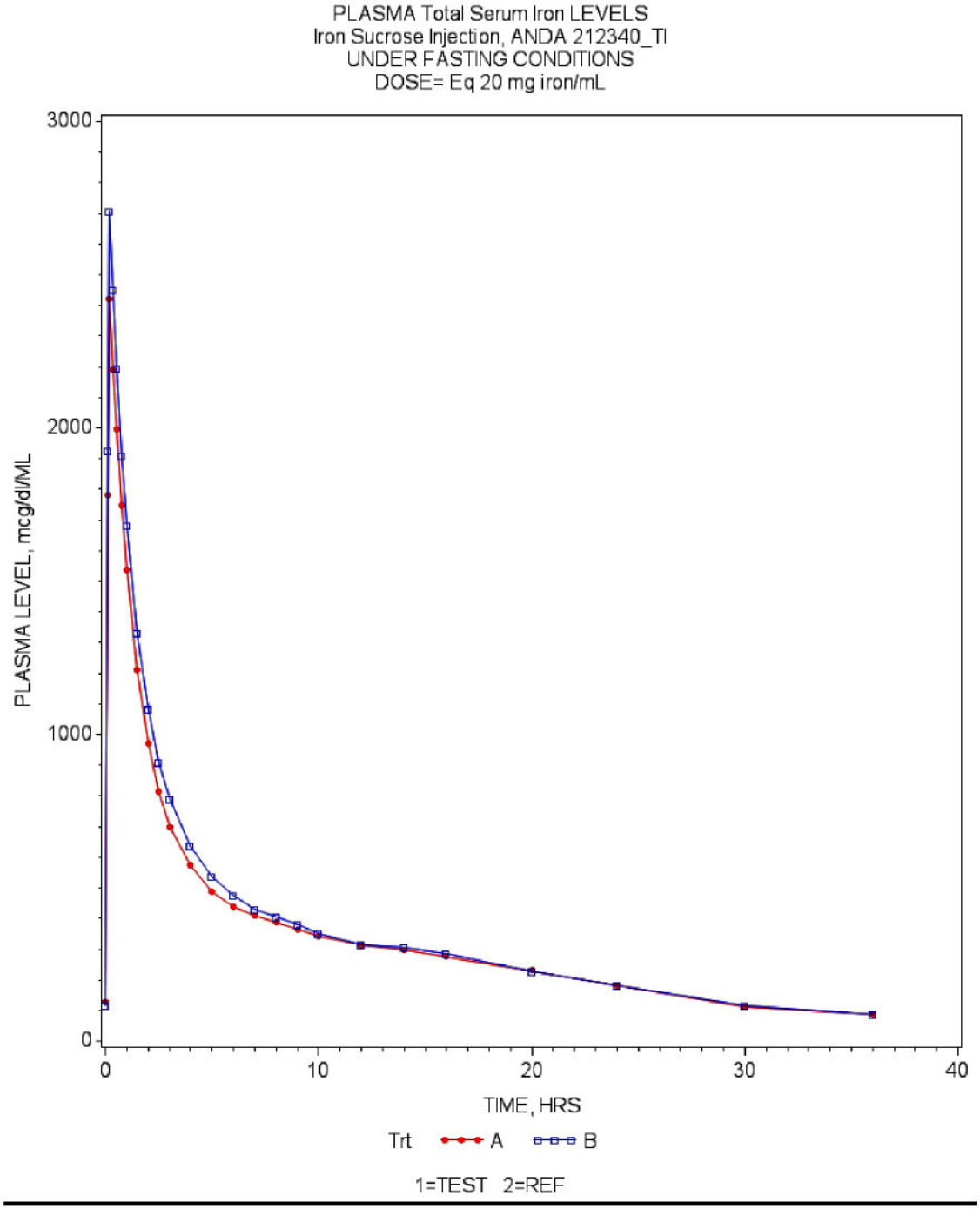
Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

TI-TBI*

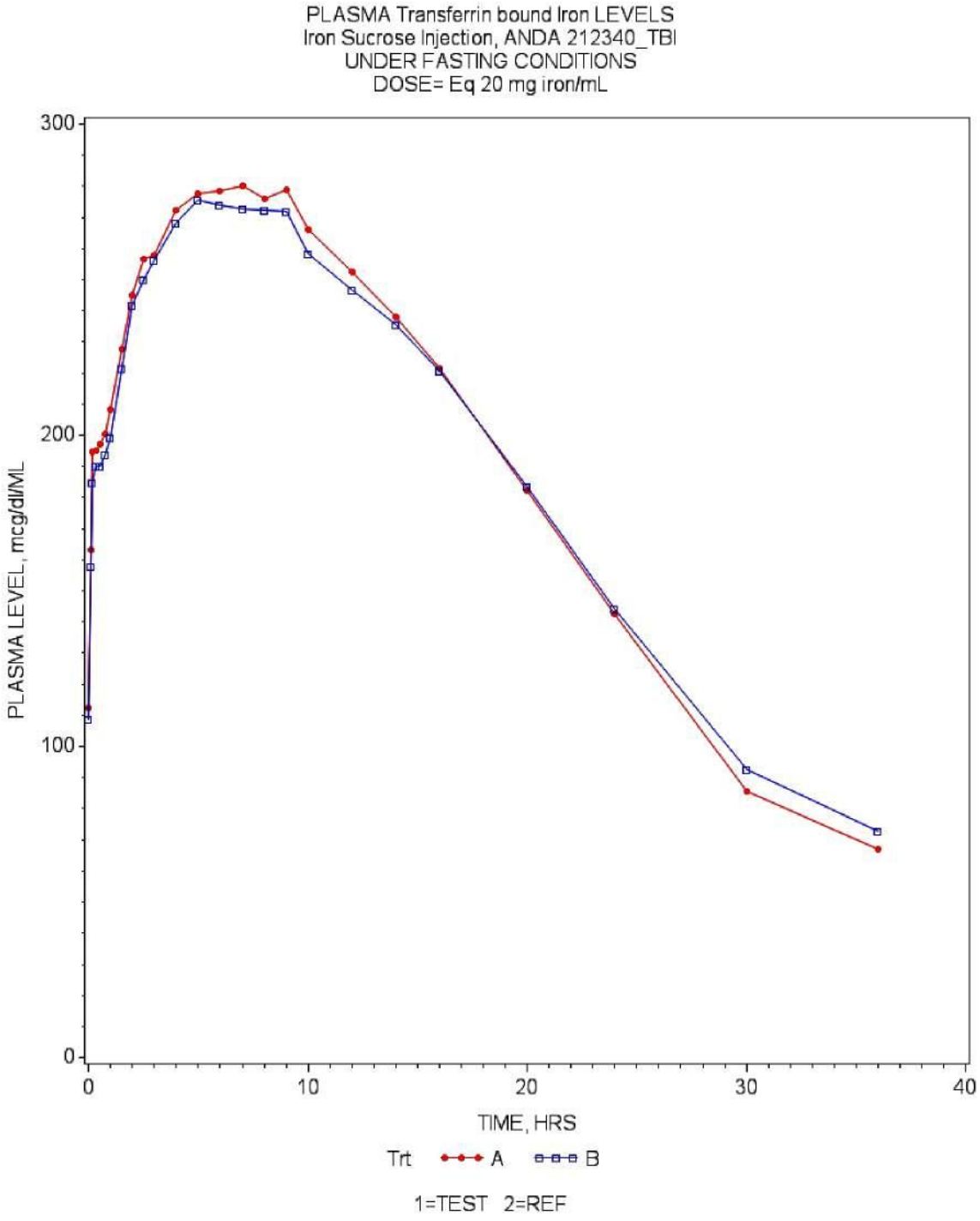
	MEAN1	CV1	MEAN2	CV2	RMEAN12
TIME HR					
0	17.42	70.36	13.30	99.23	1.31
0.08	1616.28	32.00	1780.03	36.99	0.91
0.17	2225.22	17.63	2519.76	18.03	0.88
0.33	1992.97	17.70	2260.02	17.60	0.88
0.5	1799.39	18.50	2004.43	17.95	0.90
0.75	1545.35	19.53	1715.42	19.07	0.90
1	1327.17	21.37	1483.26	20.66	0.89
1.5	981.96	24.30	1108.50	21.93	0.89
2	726.28	26.54	840.70	24.23	0.86
2.5	559.82	28.06	661.01	26.28	0.85
3	440.62	27.95	531.47	26.16	0.83
4	303.91	29.63	370.08	29.70	0.82
5	210.68	32.79	263.62	31.92	0.80
6	160.92	30.23	201.54	32.33	0.80
7	131.37	33.38	160.51	31.47	0.82
8	112.57	33.31	133.76	34.04	0.84
9	88.21	38.55	110.83	58.79	0.80
10	77.99	41.01	95.26	58.49	0.82
12	63.15	44.79	69.82	70.97	0.90
14	61.71	48.75	71.00	50.53	0.87
16	54.84	50.12	63.99	51.02	0.86
20	48.97	58.55	48.09	69.25	1.02
24	41.25	57.57	38.56	50.52	1.07
30	31.91	77.53	30.66	81.35	1.04
36	26.95	64.94	23.75	67.63	1.13

Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

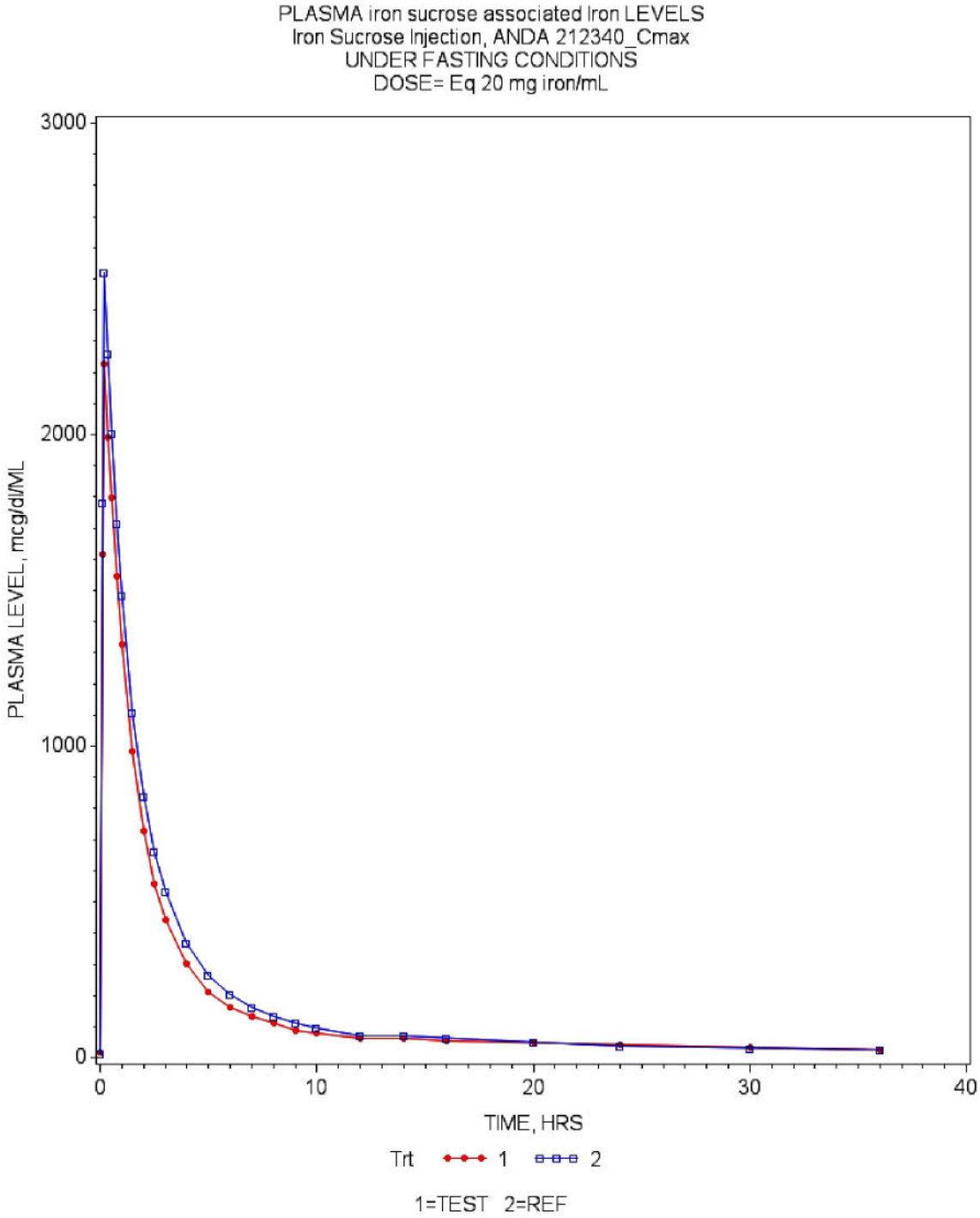
TI



TBI


PLASMA Transferrin bound Iron LEVELS
Iron Sucrose Injection, ANDA 212340_TBI
UNDER FASTING CONDITIONS
DOSE= Eq 20 mg iron/mL
PLASMA LEVEL, mcg/dl/ML
300
200
100
0
0
10
20
30
40
TIME, HRS
Trt A B
1=TEST 2=REF

TI-TBI (Iron Sucrose associated iron)



4.1.2 *In Vitro* Bioequivalence Study

4.1.2.1 Study Design

4.1.2.1.1.1 Study Information

Study Number	IRSUS_PRT_DLS_IVC_V03 (Module 3.2.P.2)
Study Title	In Vitro Characterization Report of Drug Product: Particle Size Distribution
Clinical Site (Name & Address)	N/A
Principal Clinical Investigator	N/A
Dosing Dates	N/A
Analytical Site (Name & Address)	(b)(4)
Analysis Dates	3/18/2019 (study report date)
Principal Analytical Investigator	(b)(4)
Sample Storage : **(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)** **(b) Temperature Range (e.g., -20°C to -80°C)**	N/A
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	N/A

4.1.2.1.1.2 Product Information

Table 2: Sampling testing

(b)(4)

For each product, ten (10) separate vials of the drug product are used and three (3) preparations per vial were made. Two (2) measurements per preparation were performed and the results are reported as arithmetic average of two (2) measurements for each preparation. The applicant will be asked to provide individual measurement data to make sure the method precision.

(b)(4)

(b)(4)

(b)(4)

(b)(4)

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(b)(4)

(b)(4)

4.1.2.3 Geometric Means and 90% Upper Bound - Assessor Calculated

***Assessor's note:** The statistical analyses including variability calculation and PBE analysis are not performed due to missing SAS dataset for PSD study.

Reviewer's Comments: Inadequate

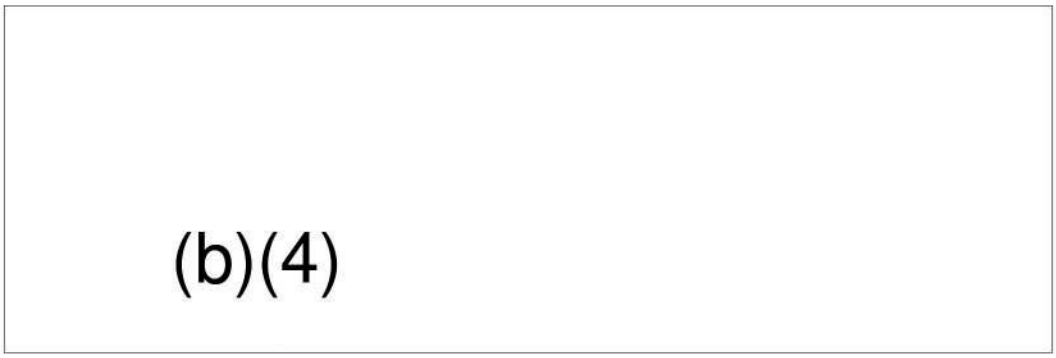
1. The applicant used five (5) batches of test product and five batches of reference product in PSD study. Ten separate vials of each drug product were used and three preparations per vial were made and two measurements per preparation were performed and the results were reported as arithmetic average of two (2) measurements for each preparation. Based on the applicant's calculation using five batches, the test product meets PBE criteria for PSD study. However, the applicant did not submit the method validation SOP, and SAS dataset for *in vitro* particle size distribution study by dynamic light scattering in the submission dated 8/28/2019. The PSD study will be further assessed after the submission of the data.

2. The applicant did not give the exact date of PSD study, but the study report is prepared in 3/18/2019. The assessor noticed two test product batches (Nos. IRSUS/22 and IRSUS/25) are demo batch manufactured in Dec. 2017[55]. The other three exhibit batches including bio-lot (#801859) were manufactured in June. 2018. The applicant only submitted up to six months stability testing data in current application. The applicant will be asked to provide study date for PSD study.

3. Based on the applicant provided batch information, the test products are manufactured by different batches of API: (b)(4). The assessor understands that the API manufacturer (b)(4) has manufactured numerous batches of API (b)(4) (b)(4) In Agency's pre-ANDA meeting response to the applicant, the applicant was asked to use at least three batches of the RLD, and three batches of test drug substance manufactured by the intended commercial process to perform drug substance physicochemical property characterization studies[57]. The applicant will be asked to clarify if there is any difference among all five test product batches (IRSUS/22, IRSUS/25, 801859, 801863, and 801869) in terms of , manufacturing process, in-process controls and specifications.

4. Per applicant submitted protocol "In vitro characterization/Particle size distribution testing; effective date: January 14, 2019)", the particle size measurements were performed by using (b)(4) The sample was prepared using procedure as below:

[55] \\cdsesub1\evsprod\anda212340\0001\m3\32-body-data\32p-drug-prod\iron-sucrose-injection-rafarm-sa\32p2-pharm-dev\invitro-characterization-dp.pdf; page 17/328
[56] EDR, ANDA 212340, Module 2.3.P, Drug product. Pdf, Page 11/95.
[57] GDRP, ANDA 212340-PDEV-Meeting-00197, Send final meeting minutes, Jeffrey Tworzyanski, 1/9/2019



5. 

6. 

4.1.2.4 Overall Comment

Was the in vitro bioequivalence study acceptable? Inadequate.

[58] DARRTS, ANDA 203639, Lerman Bruce J, 8/29/2014, Rev-Bioeq-21 (Primary Review), Archive
[59] DARRTS, ANDA 202311, Lu Dongmei, 11/28/2012, Rev-Bioeq-01 (General Review), Archive

4.2 Formulation Data

4.2.1 Test Formulation

Unit Dose Composition of Iron Sucrose Injection, 50mg/2.5mL:

Ingredient	Function	Amount per mL	Amount per vial	% w/v	IIG[1] Limit (Injection)
Iron Sucrose	Active Pharmaceutical Ingredient	20 mg elemental iron	50 mg elemental iron	(b)(4)	
Sodium Hydroxide, NF	pH adjustment	q.s. to pH 10.5 – 11.1	q.s. to pH 10.5-11.1		
Water for Injection, USP	(b)(4)				

Unit Dose Composition of Iron Sucrose Injection, 100mg/5mL:

Ingredient	Function	Amount per mL	Amount per vial	% w/v	IIG[1] Limit (Injection)
Iron Sucrose	Active Pharmaceutical Ingredient	20 mg elemental iron	100 mg elemental iron	(b)(4)	
Sodium Hydroxide, NF	pH Adjustment	q.s. to pH 10.5 – 11.1	q.s. to pH 10.5-11.1		
Water for Injection, USP	(b)(4)				

Unit Dose Composition of Iron Sucrose Injection, 200mg/10mL:

Ingredient	Function	Amount per mL	Amount per vial	% w/v	IIG[1] Limit (Injection)
Iron Sucrose	Active Pharmaceutical Ingredient	20 mg elemental iron	(b)(4)	(b)(4)	
Sodium Hydroxide, NF	pH Adjustment	q.s. to pH 10.5 – 11.1	q.s. to pH 10.5-11.1		
Water for Injection, USP	(b)(4)				

1.12.15 Request for Waiver

Formulation:

Ingredient	50 mg/2.5 mL		100 mg/5 mL		200 mg/10 mL	
	Amount per mL	% w/v	Amount per mL	% w/v	Amount per mL	% w/v
Iron Sucrose	Equivalent to 20 mg Elemental Iron Fe(III)	(b)(4)	Equivalent to 20 mg Elemental Iron Fe(III)	(b)(4)	Equivalent to 20 mg Elemental Iron Fe(III)	(b)(4)
Sodium Hydroxide, NF	q.s. to pH 10.5-11.1	q.s.	q.s. to pH 10.5-11.1	q.s.	q.s. to pH 10.5-11.1	q.s.
Water for Injection, USP	(b)(4)					
(b)(4)						

(b)(4)

4.2.2 RLD Formulation[60]

(NOT TO BE RELEASE UNDER FOIA)

(b)(4)

Comments on Formulation:

- The current draft product specific BE guidance for Iron Sucrose Injection recommends that the test product should be qualitatively (Q1)/quantitatively (Q2) the same as the RLD[61]. The applicant submitted control #139879 to request to verify the acceptability of their proposed formulation for Iron Sucrose Injection, EQ 20 mg base/mL[62]. The current test formulation is the same as the one proposed in control #139879. The test product is Q1 and Q2 the same as RLD.

- Per PSG on this drug product[63], the applicant also needs to establish the equivalence in the stoichiometric ratios of iron, sucrose, and other relevant components need to be established. The applicant needs to conduct in vitro characterization to establish the sameness in the physicochemical properties. The applicant submitted in vitro characterization study report in Module 3.2.P.2, and the office of pharmaceutical quality will review these data.

- (b)(4)

[61] https://www.accessdata.fda.gov/drugsatfda_docs/psg/Iron_sucrose_inj_21135_RV11-13.pdf
[62] https://panorama.fda.gov/task/view?ID=5530eacd00b948b929ca59ff003e0c92
[63] https://www.accessdata.fda.gov/drugsatfda_docs/psg/Iron_sucrose_inj_21135_RV11-13.pdf
[64] RLD VENOFER® label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021135s035lbl.pdf

- The applicant also submitted the formulation for 50 mg/2.5 mL and 200 mg/10 mL strength. Per PSG[65], waiver request for in vivo testing can be applied to these two strengths product based on (i) acceptable bioequivalence studies on the 100mg/5mL strength; and (ii) proportional similarity of the formulations across all strengths.

- The test product formulations for 50 mg/2.5 mL and 200 mg/10 mL are proportionally similar to the bio-strength 100 mg/5 mL. However, the in vivo study waiver is not granted due to inadequate BE study on 100 mg/5 mL strength.

- The applicant's formulation is **acceptable**.

[65] https://www.accessdata.fda.gov/drugsatfda_docs/psg/Iron_sucrose_inj_21135_RV11-13.pdf

4.3 Attachments

4.3.1 Additional Study

Are there any additional studies? (e.g. pilot , failed) **If yes, please provide the location of report (complete/summary)**	☒ Yes ☐ No
Number of Subjects	36 (12 per treatment arm)
Are the test formulations in the pilot/failed studies and pivotal studies similar[66]?	☒ Yes ☐ No ☐ N/A
What was the objective of pilot/failed study?	To evaluate bioequivalence for two test product formulations vs RLD VENOFER® (iron sucrose) Injection, 100 mg/5 mL.
Please comment on reason(s) of failure	See comments below
Any serious adverse events or deaths reported?	☐ Yes ☒ No

[66] Submission of Summary Bioequivalence Data for Abbreviated New Drug Applications

Pilot Fasting Study (No. RFR-P5-810)

Total Iron

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: Mean (Range)	Mean Parameters (%CV)						Study Report Location
					Cmax [a] (µg/dL)	Tmax [ab] (hr)	AUC0-t [a] (µg•h/dL)	AUC∞ [c] (µg•h/dL)	T½ [c] (hr)	Kel [c] (hr-1)	
RFR-P5-810	Single Dose Parallel Comparative Bioavailability Pilot Study of Iron Sucrose 20 mg/mL Intravenous Infusion in Healthy Male and Female Volunteers Following the Infusion of a 100 mg Dose/Fasting State	Randomized single-dose parallel	**Test-1:** Iron sucrose USP injection, intravenous 100 mg/5 mL i.v. Lot B260396 **Test-2:** Iron sucrose USP injection, intravenous 100 mg/5 mL Lot B260397 **Reference:** Venofer® (iron sucrose) 100 mg/5 mL intravenous injection i.v. Lot 5351A	36 completing (22/14) Healthy subjects 36 (22-50)	2528.5 (24.6%) 2372.0 (15.9%) 2619.6 (17.7%)	0.17 (0.08 - 0.17) 0.17 (0.08 - 0.17) 0.17 (0.17)d	12177.4 (25.1%) 11590.6 (21.5%) 12052.3 (26.3%)	12359.9 (23.1%) 12555.0 (18.6%) 14001.1 (27.0%)	8.11 (23.2%) 7.82 (27.8%) 10.62 (31.1%)	0.0899 (24.0%) 0.0956 (30.3%) 0.0722 (34.8%)	5.3.1.2

a n= 12 for the Test-1, the Test-2 and the Reference (RFR-P5-810)
b Median (range) is presented.
c n=9 for the Test-1, n=9 for the Test-2 and n=11 for the Reference (RFR-P5-810)

Transferrin-Bound Iron

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: Mean (Range)	Mean Parameters (%CV)						Study Report Location
					Cmax [a] (µg/dL)	Tmax [ab] (hr)	AUC0-t [a] (µg•h/dL)	AUC∞ [c] (µg•h/dL)	T½ [c] (hr)	Kel [c] (hr-1)	
RFR-P5-810	Single Dose Parallel Comparative Bioavailability Pilot Study of Iron Sucrose 20 mg/mL Intravenous Infusion in Healthy Male and Female Volunteers Following the Infusion of a 100 mg Dose/Fasting State	Randomized single-dose parallel	**Test-1:** Iron sucrose USP injection, intravenous 100 mg/5 mL Lot B260396 **Test-2:** Iron sucrose USP injection, intravenous 100 mg/5 mL Lot B260397 **Reference:** Venofer® (iron sucrose) 100 mg/5 mL intravenous injection Lot 5351A	36 completing (22/14) Healthy subjects 36 (22-50)	315.4 (19.3%) 330.5 (22.6%) 317.7 (23.9%)	6.00 (2.50 - 14.00) 7.50 (4.00 - 12.00) 6.00 (5.00 - 10.00)	6569.3 (30.7) 6926.2 (26.3%) 6393.4 (31.9%)	8398.9 (29.7) 8560.2 (24.3%) 7767.0 (29.4%)	9.64 (28.5%) 8.87 (37.1%) 8.86 (24.1%)	0.0772 (26.9%) 0.0899 (39.4%) 0.0823 (23.2%)	5.3.1.2

a N=12 for Test 1, Test 2 and Reference,
b Median (range) is presented.

Maximum concentration value and AUC of the Difference between Total Iron and Transferrin-Bound Iron

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: Mean (Range)	Mean Parameters (%CV)			Study Report Location
					Maximum value of the difference in concentration between TI and TBI [a] (µg/dL)	Difference in AUC0-T between TI and TBI [a] (µg•h/dL)	Difference in AUC0-∞ between TI and TBI [b] (µg•h/dL)	
Pilot Study RFR-P5-810	Single Dose Parallel Comparative Bioavailability Pilot Study of Iron Sucrose 20 mg/mL Intravenous Infusion in Healthy Male and Female Volunteers Following the Infusion of a 100 mg Dose/Fasting State	Randomized single-dose parallel	**Test-1:** Iron sucrose USP injection, 100 mg/5 mL i.v. inj. Lot B260396 **Test-2:** Iron sucrose USP injection, intravenous 100 mg/5 mL Lot B260397 **Reference:** Venofer® (iron sucrose) 100 mg/5 mL i.v. inj. Lot 5351A	36 completing (22/14) Healthy subjects 36 (22-50)	2225.9 (16.6) 2171.5 (16.5%) 2371.1 (16.0)	5608.0 (27.5) 4664.4 (21.6%) 5658.9 (24.7%)	5601.4 (18.5%) 4496.2 (23.2%) 6497.7 (31.1%)	5.3.1.2

a n= 12 for the Test-1, the Test-2 and the Reference for the pilot study
b n= 8 for the Test-1, n= 9 for the Test-2 and n= 10 for the Reference for the pilot study

Reviewer's Comments:

- The pilot study No. RFR-P5-810 was previously submitted in Pre-ANDA meeting package for ANDA 212340, and the pilot BE study has been reviewed in DBIII's response to consult request[67].

- Based on the applicant's statement in original development meeting request dated Aug. 6, 2018[68], although results from all the physicochemical characterization of the final API and final drug product indicated that there is no differences between the Test-1 and Test-2, comparing to the RLD, there was a difference in the

(b)(4)

Synopsis of pilot study

Pilot Synopsis.pdf

Pilot study report

pilot study report.pdf

[67] GDRP, ANDA 212340-PDEV-Meeting-00197, Respond to Consult Request, Yun Wang (4), 11/29/2018
[68] GDRP, ANDA 212340-PDEV-Meeting-00197, FDA meeting Request Package_Final, 8/6/2018
[69] GDRP, ANDA 212340-PDEV-Meeting-00197, Send Final Meeting Minutes, 1/9/2019

4.3.2 DCR Consult Response dated 1/29/2020[70]

A212340_0_DCR_Cli
nical _Safety_Iron Su

The BE assessor agrees with the DCR assessor's conclusions as below:

1. These SAEs are unlikely related to the proposed ANDA product or its formulation. Hence it does not indicate any safety or quality concern.
2. No additional information or action is needed from the firm.

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[70] GDRP, ANDA 212340-Bioequivalence IR and Consults, Respond to Consult Request, 1/29/2020

4.3.3 SAS Output

Study	SAS Data	SAS Code	SAS Output/Table
Fasting	TI-TBI (Cmax calculation)  212340 Cmax TI AUC-TBI AUC  212340 DAUC	TI-TBI (Cmax)  206604 Iron I TI AUC-TBI AUC  212340 Iron I	TI-TBI (only for Cmax)  212340 Cmax TI AUC-TBI (AUC)  212340 DAUC

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA:	212340
APPLICANT:	Sandoz Inc.
DRUG PRODUCT:	Iron Sucrose Injection, Eq. 20 mg base/mL (50 mg/2.5 mL, 100 mg/5 mL, 200 mg/10 mL)

The Division of Bioequivalence III (DBIII) has completed its review and has identified the following deficiencies:

Deficiency Related to the Pivotal Fasting Bioequivalence Study(#RFR-P5-709):

1. You rejected analytical batches for both total serum iron and transferrin-bound iron assays based on "The coefficient of determination was [redacted]. However, this criterion was not documented in your standard operation procedure (SOP) [redacted]. Please provide evidence to support why you pre-set [redacted] as R^2 cutoff.

Deficiencies Related to Particle Size Distribution (PSD) Study:

1. Please submit SOP for method validation of PSD study by dynamic light scattering. Please also provide study date for your PSD study.

2. You used five test product batches (two demo batches: #IRSUS/22, IRSUS/25; three exhibit batches: 801859, 801863, and 801869) in PSD study. Please clarify if there is any difference among all five test product batches,) in terms of manufacturing process, in-process controls and specifications.

3. You used test product (lot #IRSUS/25, 2017 demo batch) to conduct pre-study method validation for precision (Study report No. IRSUS_AMV_REP_DP_DLS_V01). Since the test product is not an approved drug product at the time of submission, it is not appropriate to be used in method validations. Please repeat pre-study method validation for precision, intermediate precision, repeatability and ruggedness using the reference product.

4. For PSD study by dynamic light scattering, you stated that you performed two measurements per preparation and reported the results as arithmetic average of two measurements for each preparation. Please provide in vitro testing data with every individual measurement in SAS transport file (.xpt) using the following format.

PRODUCT	LOT	VIAL/Measurement		D10	D50	D90	SPAN	Polydispersity Index
TEST	1234	1	Measurement 1					
			Measurement 2					
		1	Measurement 1					
			Measurement 2					
		1	Measurement 1					
			Measurement 2					
		2	Measurement 1					
			Measurement 2					
		2	Measurement 1					
			Measurement 2					
		2	Measurement 1					
			Measurement 2					
		n	Measurement 1					
			Measurement 2					
		n	Measurement 1					
			Measurement 2					
		n	Measurement 1					
			Measurement 2					

Sincerely yours,

{See appended electronic signature page}

April C. Braddy, Ph.D., RAC
Acting Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

5 OUTCOME

COMPLETED ASSIGNMENT FOR 212340 ID: 40991

Reviewer: Yun, Wang **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Iron Sucrose Injection, USP, Eq. 20 mg base/mL (50 mg/2.5 mL, 100 mg/5 mL, 200 mg/10 mL), Sandoz Inc

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Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
40991	8/29/2019	BIO	ANDA Original [1]	1	1
40991	8/29/2019	Parallel	Fasting Study [1]	1	1
40991	8/29/2019	Parallel	Fasting Study (Additional Analyte) [0.25]	0.25	0.25
40991	8/29/2019	Parallel	In Vitro Studies (Other: IVIVC, IVPT, IVRT, GSD, QCRT) (Per study for all strengths) [1]	1	1
40991	8/29/2019	Parallel	Pilot and Failed Full Extra Study for the Same Formulation as the Proposed Formulation (as defined in Guidance) [0.25]	0.25	0.25
40991	8/29/2019	Parallel	Pre-Screening [0.25]	0.25	0.25
				Total:	3.75

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 212340

OTHER REVIEW(s)

Division of Nonmalignant Hematology

Summary Safety Review

NISS #	1004594
Products:	Ferrlecit (sodium ferric gluconate complex), Venofer (Iron Sucrose), INFeD (Iron Dextran), Feraheme (ferumoxytol)
Safety Issue:	IV iron products and Kounis Syndrome
Reviewer	Rosanna Setse, MD, PhD. Deputy Division Director, Safety
Review Date	June 13, 2022

Background:

In July 2021, DNH received a Changes Being Effected (CBE) Supplement (NDA 020955 SUPPL-020) from Sanofi notifying the Agency that the Warnings and Precautions and adverse Reactions sections of the label for Ferrlecit [sodium ferric gluconate complex (SFGC)]- had been revised to include the term Kounis syndrome in the Warnings and Precautions section (5.1) and the postmarketing section (6.2). These revisions were triggered by the EMA's Pharmacovigilance Risk assessment Committee (PRAC) assessment report dated 31 October 2019, which concluded that there is a causal relationship between the use of IV iron products and occurrence of Kounis syndrome.

On September 7, 2021, DNH consulted the Division of Pharmacovigilance (DPV) and requested for a search of the FAERS database to assess whether there is a causal association between kounis syndrome and IV iron products and provide labeling recommendations for DNH consideration.

Summary of DPV Review:

A tiered case definition for Kounis syndrome corresponding to the three literature described variants of Kounis Syndrome (Kounis 2016) was used. These case definitions rely on imaging and laboratory findings (Tier A), or a combination of imaging or laboratory findings and clinical features (Tier B).

DPV searched the FAERS database with the strategy described below:

Date of search	October 4, 2021
Time period of search	All dates through October 3, 2021
Search type	Drug Safety Analytics Dashboard (DSAD) Quick Search
Product terms	Product Active Ingredient: Iron dextran; iron sucrose; ferric carboxymaltose; ferric derisomaltose; sodium ferric gluconate complex; ferumoxytol; ferumoxytol non-stoichiometric magnetite
MedDRA search terms (Version 24.0)	SMQ - *Ischaemic heart disease* (narrow search) PT - *Vascular stent thrombosis*
* See Appendix A for a description of the FAERS database. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, SMQ=Standardised MedDRA Query, PT=Preferred Term	

The FAERS search retrieved 174 reports. After applying the case definition for Kounis syndrome and accounting for duplicate reports, four cases were included in the case series of Kounis Syndrome reported with IV iron use. Two of the four cases were also literature reports (Ahluwalia et al. 2004; Hao et al. 2014).

All four cases in the series provided elements sufficient for inclusion under Tier B of the case definition None provided Tier A evidence of Kounis Syndrome following exposure to IV iron products. Only one case was assessed as "probable" using the WHO-UMC causality assessment system, and only one case involved Ferrlecit.

FAERS Line Listing of Kounis Syndrome with Iv Iron Products Case Series (N=4)

Ref #	FAERS Case #	Initial FDA Received Date	Version #	Manufacturer Control #	Report Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
1	6920633 [5793538] [7242745]	02/12/2009	1	20090038 [2005-01398] [20090583]	Expedited	37	Female	USA	HO
2	9670358	11/04/2013	2	AMAG201300187	Expedited	70	Male	Canada	DE, HO, LT, OT
3	10238870	06/12/2014	1	20140321	Expedited	57	Male	China	HO, LT
4	11228784	06/29/2015	1	Not applicable	Direct	63	Female	USA	LT, OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A case can have more than one serious outcome.
Abbreviations: DE=death, HO=hospitalization, LT= life-threatening, OT=other medically significant

Two cases are summarized below: one is the only case assessed as "probable" using the WHO-UMC causality assessment system and the other is the only case involving sodium ferric gluconate complex (Ferrlecit).

FAERS Case # 10238870, iron sucrose, China, Expedited

A 57-year-old man with iron-deficiency anemia (supporting labs not reported) was prescribed IV iron sucrose as an outpatient. No other concurrent medications were reported. During the first iron sucrose infusion, the patient complained of dyspnea, malaise, and sweating. The same symptoms recurred upon receiving his second dose, but the dyspnea was more severe and his condition "quickly deteriorated" with continuous coughing, pink frothy sputum, hypotension and tachycardia (140 bpm). He was admitted to the hospital, received dopamine and norepinephrine. His pulse rate was approximately 96 bpm; blood pressure of 60/40 mmHg; and oxygen saturation was 70-75%." Cardiac troponin I levels were elevated "above 50 µg/L" (exact level not reported [NR]; reference range 0-0.15 µg/L). Electrocardiogram (ECG) showed ST-segment elevation in leads I and aVL. He was diagnosed with acute ST-segment elevation myocardial infarction (STEMI) and cardiogenic shock. Coronary angiography revealed a 70-80% diffuse lesion in the mid-distal end of the left circumflex artery (LCx) with TIMI grade 3 flow "which corresponded to the lateral wall infarction indicated by ECG [electrocardiogram] and echocardiogram;" No lesions were found in the left main coronary artery (LMCA), right coronary artery, or left anterior descending (LAD) artery. Following rehydration and treatment with an unspecified vasoactive agent, the patient's condition stabilized, and ECG showed ST-segment regression on hospital admission day 2. Circulating IgE levels were within normal limits when tested on day 8 of hospitalization, at 56.42 international units (IU)/milliliter (mL) (reference range 1.27-241.3 IU/mL). Chest CT showed decreased pulmonary exudation on admission day 14. No lesions were found upon repeat coronary angiography on admission day

24, and the diffuse lesion previously noted in the LCx had disappeared. The patient was discharged on admission day 25.

Causality assessment: DNH assessed this case as **probably** associated with iron sucrose use due to: – the temporal association of drug intake with onset of symptoms, the absence of other factors or history that suggest a history of CAD and normal coronary arteries other than the diffuse vasospasm noted in the left circumflex artery; evidence of more severe symptoms on re-challenge and symptoms consistent with anaphylaxis.

FAERS Case # 11228784, sodium ferric gluconate complex (Ferrlecit), USA

A 63-year-old woman received 250mg Ferrlecit IV over two hours for microcytic anemia with iron deficiency. Her past medical history included coronary artery disease (CAD) with three stents, hypertension, hyperlipidemia, peripheral artery disease, depression, tobacco use, and gastrointestinal bleeding. Her reported allergies included penicillin (swelling), strawberries (swelling). Reported concomitant medications were aspirin, clopidogrel, metoprolol tartrate, lisinopril, atorvastatin, pantoprazole, venlafaxine, lamotrigine, baclofen, and furosemide. Approximately 1.5 hours into the Ferrlecit infusion, she developed hives and itching and was treated with diphenhydramine and famotidine. She then became hypotensive and diaphoretic with cool extremities. IV fluids were administered with stabilization of her systolic blood pressure. An EKG revealed ST segment elevations (leads not reported). Left heart catheterization revealed in-stent thrombosis and the patient received a drug-eluting stent to the LAD artery. The patient had no further events.

Causality assessment: DNH assessed this case as **possibly** associated with Ferrlecit use due to the temporal association of Ferrlecit administration with the events of hives and itching which are consistent with clinical manifestations of a hypersensitivity reaction. The association between IV iron use and hypersensitivity reactions/anaphylaxis is well recognized. The evidence to support a causal association between Ferrlecit and the observed cardiac event in this case is however confounded by the patient's history of CAD with multiple prior stents, history of tobacco use and other risk factors such as , hypertension, hyperlipidemia, peripheral artery disease which provide possible alternative etiologies for the event of stent thrombosis. The reported event of hypotension could be associated with a cardiac or hypersensitivity event, however this occurred after administration of diphenhydramine which is also independently associated with hypotension.

Periodic Safety Reports

DPV also screened the most recent PSRs from NDA holders of the following IV iron products to identify applicants that are assessing Kounis Syndrome with IV iron use, and for product use estimates:

- INFeD (iron dextran) NDA 017441 Periodic Adverse Drug Experience Report (PADER), October 11, 2020 – October 10, 2021 (Allergan 2021a)
- Venofer (iron sucrose) NDA 021135 PADER, November 7, 2020 – November 6, 2021 (American Regent 2021b)
- Feraheme (ferumoxytol) NDA 022180 Periodic Safety Update Report (PSUR), July 1, 2020 – June 30, 2021 (Covis 2021)
- Injectafer (ferric carboxymaltose) NDA 203565 PADER, July 26, 2020 – July 25, 2021 (American Regent 2021c)

- Monoferric (ferric derisomaltose) NDA 208171 PADER, July 16, 2021 – October 15, 2021 (Pharmacosmos 2021)

One PSR (for Injectafer (ferric carboxymaltose) NDA 203565 (American Regent 2021c) screened by DPV included an assessment of an IV iron product and Kounis Syndrome. The Applicant (American Regent) identified one report with the PTs Kounis Syndrome and Acute coronary syndrome in a 65-year-old male patient who experienced retrosternal pain, profuse sweating, and asthenia during his second infusion (a 500mg bolus) of ferric carboxymaltose. Confounding factors included this patient's medical history of arterial hypertension and dyslipidemia as well as concomitant medications of ramipril (Triatec) and atorvastatin calcium (Torvast). The patient was reported to have recovered from the event although remedial treatment was unspecified. This case was also identified by DPV's FAERS search (FAERS ID 18864189). The report described imaging findings of normal coronary arteries; however, it did not meet the DPV's case definition because laboratory evidence or clinical features strongly compatible with laboratory evidence (defined in Tier A of the DPV case definition) was not provided. The remaining PSRs screened by DPV did not include an assessment of IV iron products and Kounis Syndrome.

FDA Label Search

An FDA label search by DPV found that Ferrlecit was the only drug product with the term 'Kounis Syndrome' in its labeling.

Review Comments:

Kounis syndrome has been defined as the concurrence of acute coronary syndromes including coronary spasm, acute MI, and stent thrombosis, with conditions associated with mast cell activation, such as allergies or hypersensitivity and anaphylactic or anaphylactoid insults (Kounis N.G. et al 2011; Kounis N.G. et al. 2006). The possible mechanism involves the release of inflammatory mediators through mast cell activation which induce coronary artery spasm and/or atheromatous plaque erosion or rupture. Others have described Kounis syndrome as the coincidental occurrence of two distinct conditions (acute coronary syndrome and anaphylaxis) accompanied by clinical and laboratory findings of angina pectoris caused by inflammatory mediators released during an allergic insult (Biteker M. et al. 2010). Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to iron containing medicinal products for IV administration. Three variants of Kounis syndrome have been described based on the extent of a patient's pre-existing atherosclerotic disease when a hypersensitivity reaction triggers a mast cell-mediated inflammatory cascade that compromises the coronary circulation. The type I variant includes normal or nearly normal coronary arteries without risk factors for coronary artery disease (CAD). The type II variant includes culprit but quiescent preexisting atheromatous disease. The type III variant includes coronary artery stent thrombosis. The diagnosis of Kounis syndrome is based on clinical symptoms and signs as well as on laboratory, electrocardiographic, and angiographic evidence.

FDA's review of post marketing data from several sources including the FAERS database, the most recent Periodic Safety Reports for all IV iron products and the medical literature, identified 4 cases which provide some support for the specific pathological mechanism described as Kounis Syndrome in association with IV iron use. **The IV iron products involved were ferumoxytol,**

iron dextran, iron sucrose and sodium ferric gluconate complex. One case (FAERS Case # 10238870) provided reasonable evidence of a possible causal association between iron sucrose and Kounis Syndrome using the WHO-UMC Causality Assessment System. The other three cases were assessed by DPV and DNH as probably associated with IV iron use.

All the IV iron labels contain Hypersensitivity Reactions in WARNINGS AND PRECAUTIONS section, with highly similar descriptions and instructions. All IV iron products are also labeled for chest pain, chest discomfort, and/or chest tightness in the ADVERSE REACTIONS (either from clinical trial experience or postmarketing experience) section. Ferrlecit, Feraheme and INFed are also labeled with the following terms: angina pectoris, myocardial infarction (Ferrlecit); angina pectoris; ischemic myocardial events, cardiac /cardiorespiratory arrest (Feraheme); cardiac arrest (INFed). However, there are two components of Kounis syndrome (hypersensitivity reaction and ACS) and both of these are necessary to classify Kounis syndrome as a distinct clinical entity.

As noted by DPV, the term "Kounis syndrome" does not currently appear on any approved drug labeling (other than Ferrlecit) and previous DPV reviews of Kounis Syndrome have recommended an objective description of the event be placed in labeling rather than the eponym (Cotter and Woronow 2020b; Gish and Woronow 2020). *"DPV and subsequent Office of New Drugs (OND) objections to using the Kounis Syndrome eponym in labeling include: concern that the eponym may not be widely embraced or understood among U.S. healthcare providers; the term is not included in the 2020-ICD10-CM index; and debate in the medical literature about Kounis Syndrome (Cotter and Woronow 2020b; Gish and Woronow 2020; Debellas 2020; Davidson 2020; Voqui 2021)."*

Considering the above discussed concerns with the use of the term Kounis syndrome, DNH disagrees with inclusion of the term "Kounis Syndrome" in the labeling for IV iron products.

Recommended regulatory action:

1. Include an objective description of Kounis syndrome in the Ferrlecit labeling. CBE approved on 03/16/2022. See Summary Safety and Ferrlecit CBE supplement review in darrts dated 03/21/2022.

2. Issue SLR letters to the other affected IV iron products (ferumoxytol, iron dextran, iron sucrose) to include a description of Kounis syndrome in the postmarketing sections of their approved labeling.

Recommended language for description of kounis syndrome in the postmarketing section of affected IV iron products (ferumoxytol, iron dextran, iron sucrose):

> acute myocardial ischemia with or without myocardial infarction with in-stent thrombosis in the context of hypersensitivity reaction.

References

Ahluwalia MS, S Patel, H Daw. 2004. Myocardial Infarction Induced by Intravenous Iron Dextran Infusion in Absence of Coronary Artery Disease. Blood; 104(11):3694.

Cotter S, D Woronow. 2020b. Office of Pharmacovigilance and Epidemiology Integrated Review of Kounis Syndrome with Unasyn, NDA 050608. DARRTS communication date 7/10/2020.

Davidson, A. 2020. Clinical Review of Labeling Supplement NDA 50780/S-020. DARRTS communication date 12/21/2020.

Debellas C. 2021. NDA 050608 Supplement-47 Pending sNDA Information Request, Email communication. DARRTS Communication Date 9/9/2020.

Gish P, D Woronow. 2020. Pharmacovigilance Review: Cefuroxime for Injection USP and Dextrose Injection USP in the Duplex Container (NDA 50780 S-020) and Kounis Syndrome. DARRTS communication date 8/28/2020.

Hao Z, C Linzhi, H Weijian, G Zhan. 2014. Kounis Syndrome induced by administration of iron sucrose: Case report. Experimental and Clinical Cardiology; 20(1):2326-2331

Kounis, N.G., et al., Kounis syndrome: a new twist on an old disease. Future Cardiol, 2011. 7(6): p. 805-24.

Kounis, N.G., Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? Int J Cardiol, 2006. 110(1): p. 7-14.

Biteker, M., Current understanding of Kounis syndrome. Expert Rev Clin Immunol, 2010. 6(5): p. 777-88.

Soufras GD, Kounis GN, Kounis NG. Fatal anaphylactic reaction to iron sucrose in pregnancy: iron-induced Kounis syndrome?. Indian J Pharmacol. 2013;45(6):642-43.

FDA U.S. FOOD & DRUG ADMINISTRATION

Rosanna Setse

Digitally signed by Rosanna Setse

Date: 6/13/2022 11:15 AM EDT
GUID: 32022

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ROSANNA W SETSE
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Division of Nonmalignant Hematology

Summary Safety and CBE Supplement Review

NISS #	1004594
Products:	Ferrlecit (sodium ferric gluconate complex)
Safety Issue:	IV iron products and Kounis Syndrome
Reviewer	Rosanna Setse, MD, PhD. Deputy Division Director, Safety
Review Date	March 14, 2022

Background:
Ferrlecit is an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients and in pediatric patients age 6 years and older with chronic kidney disease receiving hemodialysis who are receiving supplemental epoetin therapy.

In July 2021, DNH received a Changes Being Effected (CBE) Supplement (NDA 020955 SUPPL-020) from Sanofi notifying the Agency that the Warnings and Precautions and adverse Reactions sections of the label for Ferrlecit [sodium ferric gluconate complex (SFGC)]- had been revised as follows:

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving Ferrlecit in postmarketing experience. Patients may present with shock, clinically significant hypotension, loss of consciousness, or collapse. Monitor patients for signs and symptoms of hypersensitivity during and after Ferrlecit administration for at least 30 minutes and until clinically stable following completion of the infusion. Only administer Ferrlecit when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions [see Adverse Reactions (6)].

Parenterally administered iron preparations can cause hypersensitivity reactions including serious and potentially fatal anaphylactic/anaphylactoid reactions. Hypersensitivity reactions have also been reported after previously uneventful doses of parenteral iron complexes.

Hypersensitivity reactions can also progress to Kounis Syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to iron containing medicinal products for intravenous administration. In patients with present coronary disease or risks factors for coronary disease, Kounis Syndrome may be more severe. In

those patients, iron-containing medicinal products for intravenous administration should be used only after careful risk/benefit evaluation.

In the single-dose, postmarketing, safety study one patient experienced a life-threatening hypersensitivity reaction (diaphoresis, nausea, vomiting, severe lower back pain, dyspnea, and wheezing for 20 minutes) following Ferrlecit administration. Among 1,097 patients who received Ferrlecit in this study, there were nine patients (0.8%) who had an adverse reaction that, in the view of the investigator, precluded further Ferrlecit administration. These included one life-threatening reaction, six allergic reactions (including pruritus, facial flushing, chills, dyspnea/chest pain, and rash), and two other reactions (hypotension and nausea). Another two patients experienced (0.2%) allergic reactions not deemed to represent drug intolerance (nausea/malaise and nausea/dizziness) following Ferrlecit administration.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Cardiovascular System: hypotension (29%), hypertension (13%), syncope (6%), tachycardia (5%), bradycardia, vasodilatation, angina pectoris, myocardial infarction, pulmonary edema, Kounis Syndrome.

These revisions were triggered by the EMA's Pharmacovigilance Risk assessment Committee (PRAC) assessment report dated 31 October 2019, which concluded that there is a causal relationship between the use of IV iron products and occurrence of Kounis syndrome. Sanofi subsequently reviewed their Global pharmacovigilance database, the scientific literature, FAERs and the EudraVigilance database and concluded that the weighted cumulative evidence is sufficient to support a causal association between Kounis syndrome and SFGC. Sanofi submitted a Safety Evaluation Report to support the CBE labeling supplement.

Summary of Sanofi's Safety Evaluation Report (SER)

Sanofi's search of its global pharmacovigilance (GPV) database yielded a total of 14 relevant cases cumulatively using the following search terms:

Drug terms	Sodium ferric gluconate complex (SFGC)
Search terms MedDRA 23.1	*Ischaemic heart disease* SMQ broad
Years included in search	All reports until February 1, 2021
Additional criteria	all solicited and unsolicited cases, medically confirmed and non-medically confirmed, including diagnosis and symptoms

An e overview of the reported events in these 14 cases is shown in the Sponsor's table below:

Table: Overview of Reported Cases from Sanofi's GPV Search

Event PT	Total
Acute coronary syndrome	2
Acute myocardial infarction	4
Angina pectoris	3
Blood creatine phosphokinase increased	2
Cardiac arrest	1
Coronary artery disease	1
Coronary artery dissection	1
Myocardial infarction	4
Myocardial ischaemia	1
Myocardial necrosis marker increased	1
Total	**20***

PT: Preferred Term
*Total no. of event does not match the case count as more than one preferred term might be reported in a case.

Sanofi's search terms allowed for inclusion of cardiac events not associated with hypersensitivity reactions. Sentinel case definition used by Sanofi:

> All well documented cases that reported with Kounis Syndrome/ coronary arteriospasm/ MI [myocardial infarction] following therapy with SFGC in the presence of a plausible time-to-onset (TTO), diagnostic confirmation (electrocardiogram [ECG] or coronary angiography and laboratory confirmation for elevation of serum histamine, tryptase, troponin I) with/ without positive de-challenge and/ or rechallenge were considered sentinel."

Of the 14 identified cases, six cases reported cardiovascular adverse events secondary to hypersensitivity/ anaphylactic reactions. The remaining 8 cases were not suggestive of hypersensitivity. Further, of the 14 cases, eight cases were considered sentinel due to the presence of a highly suggestive time-to-onset and causality was assessed (by Sanofi) as possibly related to SFGC therapy due to the presence of positive temporal association in another two cases. No cases with a diagnosis of Kounis syndrome or coronary arteriospasm was reported cumulatively

Sanofi's review of the scientific literature (conducted in Medline [1966 to present] and Embase [1974 to present]) did not retrieve any publications describing Kounis syndrome following SFGC therapy. However, case reports of Kounis syndrome were identified with other IV iron preparations including iron sucrose and iron dextran [Soufras GD et al,. (2013), Zhan G et al, (2014), Ahluwalia MS et al, (2004) and Kawata AT et al, (2015)].

On September 7, 2021, DNH consulted the Division of Pharmacovigilance (DPV) and requested for a search of the FAERS database to assess whether there is a causal association between kounis syndrome and IV iron products and provide labeling recommendations for DNH consideration. DPV met with DNH on October 7, 2021 to discuss and agree on the methods applied in this review.

Summary of DPV Review:
A tiered case definition for Kounis syndrome corresponding to the three literature described variants of Kounis Syndrome (Kounis 2016) was used. These case definitions rely on imaging and laboratory findings (Tier A), or a combination of imaging or laboratory findings and clinical features (Tier B).

DPV searched the FAERS database with the strategy described below:

Date of search	October 4, 2021
Time period of search	All dates through October 3, 2021
Search type	Drug Safety Analytics Dashboard (DSAD) Quick Search
Product terms	Product Active Ingredient: Iron dextran; iron sucrose; ferric carboxymaltose; ferric derisomaltose; sodium ferric gluconate complex; ferumoxytol; ferumoxytol non-stoichiometric magnetite
MedDRA search terms (Version 24.0)	SMQ - *Ischaemic heart disease* (narrow search) PT - *Vascular stent thrombosis*
* See Appendix A for a description of the FAERS database. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, SMQ=Standardised MedDRA Query, PT=Preferred Term	

The FAERS search retrieved 174 reports. After applying the case definition for Kounis syndrome and accounting for duplicate reports, four cases were included in the case series of Kounis Syndrome reported with IV iron use. Two of the four cases were also literature reports (Ahluwalia et al. 2004; Hao et al. 2014).

All four cases in the series provided elements sufficient for inclusion under Tier B of the case definition None provided Tier A evidence of Kounis Syndrome following exposure to IV iron products. Only one case was assessed as "probable" using the WHO-UMC causality assessment system, and only one case involved Ferrlecit.

FAERS Line Listing of Kounis Syndrome with Iv Iron Products Case Series (N=4)

Ref #	FAERS Case #	Initial FDA Received Date	Version #	Manufacturer Control #	Report Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
1	6920633 [5793538] [7242745]	02/12/2009	1	20090038 [2005-01398] [20090583]	Expedited	37	Female	USA	HO
2	9670358	11/04/2013	2	AMAG201300187	Expedited	70	Male	Canada	DE, HO, LT, OT
3	10238870	06/12/2014	1	20140321	Expedited	57	Male	China	HO, LT
4	11228784	06/29/2015	1	Not applicable	Direct	63	Female	USA	LT, OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A case can have more than one serious outcome.
Abbreviations: DE=death, HO=hospitalization, LT= life-threatening, OT=other medically significant

Two cases are summarized below: one is the only case assessed as "probable" using the WHO-UMC causality assessment system and the other is the only case involving sodium ferric gluconate complex (Ferrlecit).

FAERS Case # 10238870, iron sucrose, China, Expedited

A 57-year-old man with iron-deficiency anemia (supporting labs not reported) was prescribed IV iron sucrose as an outpatient. No other concurrent medications were reported. During the first iron sucrose infusion, the patient complained of dyspnea, malaise, and sweating. The same symptoms recurred upon receiving his second dose, but the dyspnea was more severe and his condition "quickly deteriorated" with continuous coughing, pink frothy sputum, hypotension and tachycardia (140 bpm). He was admitted to the hospital, received dopamine and norepinephrine. His pulse rate was approximately 96 bpm; blood pressure of 60/40 mmHg; and oxygen saturation was 70-75%." Cardiac troponin I levels were elevated "above 50 µg/L" (exact level not reported [NR]; reference range 0-0.15 µg/L). Electrocardiogram (ECG) showed ST-segment elevation in leads I and aVL. He was diagnosed with acute ST-segment elevation myocardial infarction (STEMI) and cardiogenic shock. Coronary angiography revealed a 70-80% diffuse lesion in the mid-distal end of the left circumflex artery (LCx) with TIMI grade 3 flow "which corresponded to the lateral wall infarction indicated by ECG [electrocardiogram] and echocardiogram;" No lesions were found in the left main coronary artery (LMCA), right coronary artery, or left anterior descending (LAD) artery. Following rehydration and treatment with an unspecified vasoactive agent, the patient's condition stabilized, and ECG showed ST-segment regression on hospital admission day 2. Circulating IgE levels were within normal limits when tested on day 8 of hospitalization, at 56.42 international units (IU)/milliliter (mL) (reference range 1.27-241.3 IU/mL). Chest CT showed decreased pulmonary exudation on admission day 14. No lesions were found upon repeat coronary angiography on admission day 24, and the diffuse lesion previously noted in the LCx had disappeared. The patient was discharged on admission day 25.

Causality assessment: DNH assessed this case as **probably** associated with iron sucrose use due to: – the temporal association of drug intake with onset of symptoms, the absence of other factors or history that suggest a history of CAD and normal coronary arteries other than the diffuse vasospasm noted in the left circumflex artery; evidence of more severe symptoms on re-challenge and symptoms consistent with anaphylaxis.

FAERS Case # 11228784, sodium ferric gluconate complex (Ferrlecit), USA

A 63-year-old woman received 250mg Ferrlecit IV over two hours for microcytic anemia with iron deficiency. Her past medical history included coronary artery disease (CAD) with three stents, hypertension, hyperlipidemia, peripheral artery disease, depression, tobacco use, and gastrointestinal bleeding. Her reported allergies included penicillin (swelling), strawberries (swelling). Reported concomitant medications were aspirin, clopidogrel, metoprolol tartrate, lisinopril, atorvastatin, pantoprazole, venlafaxine, lamotrigine, baclofen, and furosemide. Approximately 1.5 hours into the Ferrlecit infusion, she developed hives and itching and was treated with diphenhydramine and famotidine. She then became hypotensive and diaphoretic with cool extremities. IV fluids were administered with stabilization of her systolic blood pressure. An EKG revealed ST segment elevations (leads not reported). Left heart catheterization revealed in-stent thrombosis and the patient received a drug-eluting stent to the LAD artery. The patient had no further events.

Causality assessment: DNH assessed this case as **possibly** associated with Ferrlecit use due to the temporal association of Ferrlecit administration with the events of hives and itching which are

consistent with clinical manifestations of a hypersensitivity reaction. The association between IV iron use and hypersensitivity reactions/anaphylaxis is well recognized. The evidence to support a causal association between Ferrlecit and the observed cardiac event in this case is however confounded by the patient's history of CAD with multiple prior stents, history of tobacco use and other risk factors such as , hypertension, hyperlipidemia, peripheral artery disease which provide possible alternative etiologies for the event of stent thrombosis. The reported event of hypotension could be associated with a cardiac or hypersensitivity event, however this occurred after administration of diphenhydramine which is also independently associated with hypotension.

DPV assessment of Sanofi's SER

Eight of the 14 cases identified by Sanofi met their sentinel case definition due to the presence of a highly suggestive time-to-onset, however only three cases reported cardiovascular adverse events secondary to hypersensitivity/anaphylactic reactions. DPV noted that, the remaining five cases reported cardiac events with no associated hypersensitivity/anaphylactic reactions; thus, they do not appear to be consistent with Kounis Syndrome. The table below (from DPV's review) summarizes the three sentinel cases from Sanofi's GPV database, after excluding the five cases identified by Sanofi that reported "cardiac events with no associated hypersensitivity/ anaphylactic reactions", and the three literature case reports identified and assessed by Sanofi, for a total of 6 cases.

Sanofi Case # or Authors/ Demography	IV Iron	Preferred Term(s) or Events	TTO/ Dechallenge/ Rechallenge/ Outcome	Risk Factors/ Confounding Factors Identified by Sanofi	DPV Reviewer Comments
Sentinel cases with cardiac events secondary to hypersensitivity/anaphylactic reactions. (n=3)					
DE01-03376/ Female	SFGC	Cardiac arrest	2 minutes/ NA/NA/ Recovered		*Does not meet DPV CD given limited information provided. Corresponding FAERS report not found.* †
200216476G DDC/ 66-yo female	SFGC	MI, blood CPK increased, myocardial necrosis marker increased	1.5 hours/ NA/NA/ Fatal	PE induced MI. Hemodialysis = increased risk of developing PE.	*Does not meet DPV CD – lacked imaging and lab findings described in CD. FAERS ID 3873060, found in DPV search. Autopsy: cause of death PE resulting in MI and GI bleed; not consistent with Kounis Syndrome etiology.*
2014SA148726/ 79-yo female	SFGC	Acute MI	Same day/ NA/NA/ Fatal	Hx of cardiac failure and HTN precluded definite causality.	*Does not meet DPV CD – lacked imaging and lab findings described in CD. FAERS ID 10570782, found in DPV search.*
Identified by Sanofi as a published case report of Kounis Syndrome. (n=3)					
Soufras GD et al. 2013/ 20-yo female	Iron sucrose	Anaphylactic shock, cardiac arrest	"following infusion"/ NA/NA/ Fatal		*Does not meet DPV CD – lacked imaging and lab findings described in CD.* ‡
Zhan G et al. 2014 (Hao et al. 2014)/ 57-yo gender NR §	Iron sucrose	Hypotension, tachycardia, hypoxemia, elevated troponin I, STEMI, cardiogenic shock, anaphylaxis, Kounis Syndrome	"following second iron sucrose admini-stration"/ NA/NA/ Recovered		*Met DPV CD and is in case series. FAERS ID 10238870.*

Periodic Safety Reports

DPV also screened the most recent PSRs from NDA holders of the following IV iron products to identify applicants that are assessing Kounis Syndrome with IV iron use, and for product use estimates:

- INFeD (iron dextran) NDA 017441 Periodic Adverse Drug Experience Report (PADER), October 11, 2020 – October 10, 2021 (Allergan 2021a)
- Venofer (iron sucrose) NDA 021135 PADER, November 7, 2020 – November 6, 2021 (American Regent 2021b)
- Feraheme (ferumoxytol) NDA 022180 Periodic Safety Update Report (PSUR), July 1, 2020 – June 30, 2021 (Covis 2021)
- Injectafer (ferric carboxymaltose) NDA 203565 PADER, July 26, 2020 – July 25, 2021 (American Regent 2021c)
- Monoferric (ferric derisomaltose) NDA 208171 PADER, July 16, 2021 – October 15, 2021 (Pharmacosmos 2021)

One PSR (for Injectafer (ferric carboxymaltose) NDA 203565 (American Regent 2021c) screened by DPV included an assessment of an IV iron product and Kounis Syndrome. The Applicant (American Regent) identified one report with the PTs Kounis Syndrome and Acute coronary syndrome in a 65-year-old male patient who experienced retrosternal pain, profuse sweating, and asthenia during his second infusion (a 500mg bolus) of ferric carboxymaltose. Confounding factors included this patient's medical history of arterial hypertension and dyslipidemia as well as concomitant medications of ramipril (Triatec) and atorvastatin calcium (Torvast). The patient was reported to have recovered from the event although remedial treatment was unspecified. This case was also identified by DPV's FAERS search (FAERS ID 18864189). The report described imaging findings of normal coronary arteries; however, it did not meet the DPV's case definition because laboratory evidence or clinical features strongly compatible with laboratory evidence (defined in Tier A of the DPV case definition) was not provided. The remaining PSRs screened by DPV did not include an assessment of IV iron products and Kounis Syndrome.

FDA Label Search

An FDA label search by DPV found that Ferrlecit was the only drug product with the term 'Kounis Syndrome' in its labeling.

Review Comments:

Kounis syndrome has been defined as the concurrence of acute coronary syndromes including coronary spasm, acute MI, and stent thrombosis, with conditions associated with mast cell activation, such as allergies or hypersensitivity and anaphylactic or anaphylactoid insults (Kounis N.G. et al 2011; Kounis N.G. et al. 2006). The possible mechanism involves the release of inflammatory mediators through mast cell activation which induce coronary artery spasm and/or atheromatous plaque erosion or rupture. Others have described Kounis syndrome as the coincidental occurrence of two distinct conditions (acute coronary syndrome and anaphylaxis) accompanied by clinical and laboratory findings of angina pectoris caused by inflammatory mediators released during an allergic insult (Biteker M. et al. 2010). Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to iron

containing medicinal products for IV administration. Three variants of Kounis syndrome have been described based on the extent of a patient's pre-existing atherosclerotic disease when a hypersensitivity reaction triggers a mast cell-mediated inflammatory cascade that compromises the coronary circulation. The type I variant includes normal or nearly normal coronary arteries without risk factors for coronary artery disease (CAD). The type II variant includes culprit but quiescent preexisting atheromatous disease. The type III variant includes coronary artery stent thrombosis. The diagnosis of Kounis syndrome is based on clinical symptoms and signs as well as on laboratory, electrocardiographic, and angiographic evidence.

FDA's review of post marketing data from several sources including the FAERS database, the data submitted by Sanofi in response to the Agency's IR, the most recent Periodic Safety Reports for all IV iron products and the medical literature, identified 4 cases which provide some support for the specific pathological mechanism described as Kounis Syndrome in association with IV iron use. The IV iron products involved were ferumoxytol, iron dextran, iron sucrose and sodium ferric gluconate complex. One case (FAERS Case # 10238870) provided reasonable evidence of a possible causal association between iron sucrose and Kounis Syndrome using the WHO-UMC Causality Assessment System. The other three cases were assessed by DPV and DNH as probably associated with IV iron use.

Sanofi's cumulative search of their GPV database for sodium ferric gluconate complex (Ferrlecit) identified eight cases that met their sentinel case definition due to the presence of a highly suggestive time-to-onset; however, as noted above, only three of the eight cases reported cardiovascular adverse events secondary to hypersensitivity/anaphylactic reactions. DNH agrees with DPV's assessment that, the remaining five cases do not appear to be consistent with Kounis Syndrome since these cases reported cardiac events with no associated hypersensitivity/ anaphylactic reactions. All the IV iron labels contain Hypersensitivity Reactions in WARNINGS AND PRECAUTIONS section, with highly similar descriptions and instructions. All IV iron products are also labeled for chest pain, chest discomfort, and/or chest tightness in the ADVERSE REACTIONS (either from clinical trial experience or postmarketing experience) section. Ferrlecit, Feraheme and INFed are also labeled with the following terms: angina pectoris, myocardial infarction (Ferrlecit); angina pectoris; ischemic myocardial events, cardiac /cardiorespiratory arrest (Feraheme); cardiac arrest (INFed). However, there are two components of Kounis syndrome (hypersensitivity reaction and ACS) and both of these are necessary to classify Kounis syndrome as a distinct clinical entity.

Sanofi identified three published case reports of Kounis Syndrome and IV iron preparations in the literature search (Ahluwalia et al. 2004; Hao Z et al 2014; Soufras et al. 2013). None of the publications described Kounis Syndrome following Ferrlecit therapy. Two of these cases met DPV's more stringent case definition of Kounis syndrome (Ahluwalia et al. 2004; Hao Z et al 2014).

As noted by DPV, the term "Kounis syndrome" does not currently appear on any approved drug labeling (other than Ferrlecit) and previous DPV reviews of Kounis Syndrome have recommended an objective description of the event be placed in labeling rather than the eponym (Cotter and Woronow 2020b; Gish and Woronow 2020). *"DPV and subsequent Office of New Drugs (OND) objections to using the Kounis Syndrome eponym in labeling include: concern that the eponym*

may not be widely embraced or understood among U.S. healthcare providers; the term is not included in the 2020-ICD10-CM index; and debate in the medical literature about Kounis Syndrome (Cotter and Woronow 2020b; Gish and Woronow 2020; Debellas 2020; Davidson 2020; Voqui 2021).”

Considering the above discussed concerns with the use of the term Kounis syndrome, DNH disagrees with Sanofi’s proposed Ferrlecit labeling revisions to include the use of the term Kounis Syndrome in the WARNINGS and PRECAUTIONS section of the Ferrlecit labeling.

Recommended regulatory action:

1. Include an objective description of the events reported rather than the term Kounis syndrome in Section 5.2 of the Ferrlecit labeling.

2. Issue SLR letters to the other affected IV iron products (ferumoxytol, iron dextran, iron sucrose) to include a description of the symptoms of Kounis syndrome in the post marketing sections of their approved labeling.

The approved the approved labeling (revisions are underlined) for Ferrlecit S20 are shown below:

6 ADVERSE REACTIONS

6.2 Postmarketing Experience

The following additional adverse reactions have been identified with the use of Ferrlecit from postmarketing spontaneous reports:

Cardiovascular System: shock, fetal bradycardia, injection site superficial thrombophlebitis, phlebitis, <u>acute myocardial ischemia with or without myocardial infarction with in-stent thrombosis in the context of hypersensitivity reaction</u>.

References

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Gish P, D Woronow. 2020. Pharmacovigilance Review: Cefuroxime for Injection USP and Dextrose Injection USP in the Duplex Container (NDA 50780 S-020) and Kounis Syndrome. DARRTS communication date 8/28/2020.

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Soufras GD, Kounis GN, Kounis NG. Fatal anaphylactic reaction to iron sucrose in pregnancy: iron-induced Kounis syndrome?. Indian J Pharmacol. 2013;45(6):642-43.

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Department of Health and Human Services
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pharmacovigilance Review

Date: February 11, 2022

Reviewers: Danielle Molnar, PharmD, BCPS, Safety Evaluator
Division of Pharmacovigilance (DPV) II

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Product Names, Application Types/Numbers, Applicants:

INFeD® (iron dextran)	NDA 017441	Allergan
Dexferrum® (iron dextran)	NDA 040024	Luitpold
Proferdex® (iron dextran)	NDA 017807	New River
Ferrlecit® (sodium ferric gluconate complex)	NDA 020955 ANDA 078215	Sanofi Aventis West-Ward Pharms
Venofer® (iron sucrose)	NDA 021135	Luitpold
Feraheme® (ferumoxytol)	NDA 022180 ANDA 206604	Amag Pharms Sandoz
Injectafer® (ferric carboxymaltose)	NDA 203565	Luitpold
Monoferric® (iron derisomaltose)	NDA 208171	Pharmacosmos

Subject: Kounis Syndrome

Submission Number: S-020 (NDA 020955)

SS ID #: 1004594

We also acknowledge DPV cardiologist Daniel Woronow, MD, FACC and Samantha Cotter, PharmD for support in applying the DPV case definition.

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports and published medical literature for an association between intravenous (IV) iron products and Kounis Syndrome. The Division of Non-Malignant Hematology (DNH) requested this review on September 7, 2021 to inform their evaluation of labeling changes submitted by Sanofi, the applicant for Ferrlecit, and to determine if labeling changes are needed for all IV iron products.

The main challenge of this review was to identify and assess postmarketing cases displaying evidence of a specific pathological mechanism - Kounis Syndrome – wherein a hypersensitivity reaction to a drug (e.g., IV iron products) causes acute inflammatory mediator release resulting in coronary artery vasospasm or plaque rupture with or without myocardial infarction or stent thrombosis.

Overall, our case series provides only limited support of the specific pathological mechanism described by Dr. Kounis as Kounis Syndrome. DPV found a possible causal association between IV iron products and Kounis Syndrome based on four cases from FAERS that met the lower tier (Tier B) of our case definition for Kounis Syndrome. We assessed the causal relationship as probable for one case, and possible for the remaining three cases using the World Health Organization-Uppsala Monitoring Center (WHO-UMC) Causality Assessment System.

While we believe the case series does little to corroborate an association between the specific mechanism of Kounis Syndrome and IV iron products, the cases do describe events associated with acute myocardial ischemia in the context of hypersensitivity reactions to IV iron products. The concurrence of events may be explained by one or more known mechanisms. Thus, a description of events rather than specific attribution of events to Kounis Syndrome may be justified in labeling of IV iron products.

Despite wide use and many years of marketing we identified only four cases of IV iron product use that may be associated with Kounis Syndrome and all four met the lower of two tiers (Tier B) in DPV's case definition. We do not feel that the level of evidence supports the placement of "Kounis Syndrome" in IV iron product labeling, but we do not object to the inclusion of an objective description of events in the ADVERSE REACTIONS, Postmarketing Experience section. DNH should consider that adding "Kounis Syndrome" to labeling would be the first inclusion of this term in any FDA approved labeling.

We prefer that any addition to labeling be limited to an objective description of the event, rather than a named syndrome that is not universally accepted in medicine and may not be commonly understood. An example of such text could be, "acute myocardial ischemia with or without myocardial infarction, or in-stent thrombosis, may occur in the context of a hypersensitivity reaction."

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports and published medical literature for an association between intravenous (IV) iron products and Kounis Syndrome. The Division of Non-Malignant Hematology (DNH) requested this review on September 7, 2021 to inform their evaluation of labeling changes submitted by Sanofi, the applicant for Ferrlecit, and to determine if labeling changes are needed for all IV iron products.[a]

1.1 BACKGROUND

On November 21, 2019, the Pharmacovigilance Risk Assessment Committee (PRAC) issued a recommendation to all Marketing Authorization Holders of IV iron products to add "Kounis Syndrome" as an undesirable effect and "There have been reports of hypersensitivity reactions which progressed to Kounis Syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction)" to the special warnings and precautions for use sections of the product information for all IV iron products (Sanofi 2020).

Sanofi submitted a Changes Being Effected (CBE) New Drug Application (NDA) Supplement-020 (NDA 020955 SUPPL-020) in July 2021 proposing to revise the existing warning for hypersensitivity reactions in WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS (AR) with the addition of Kounis Syndrome similar to what was required by the PRAC (Sanofi 2021a). Sanofi submitted a Safety Evaluation Report (SER) to support the labeling supplement and Sanofi's conclusion of an association between Ferrlecit and Kounis Syndrome (Rakshita 2021).

DNH consulted the Division of Pharmacovigilance (DPV) on September 7, 2021 to conduct a FAERS search for cases of Kounis Syndrome, to assess whether there is a causal association between Kounis Syndrome and IV iron products, and to provide labeling recommendations for consideration. DNH requested a FAERS search using a strategy broader than the Preferred Term (PT) *Kounis Syndrome* to capture cases coded with other PTs that meet the definition of Kounis Syndrome.

Kounis Syndrome

Dr. Nicholas G. Kounis defined Kounis Syndrome in 2016 as the concurrence of acute coronary syndromes (ACS) - including coronary spasm, acute myocardial infarction, and stent thrombosis - associated with acute release of eosinophils, mast cells, and platelet activation in the setting of allergic or hypersensitivity and anaphylactic or anaphylactoid insults (Kounis 2016). ("Allergic or hypersensitivity and anaphylactic or anaphylactoid insults" will be referred to as hypersensitivity reactions; and "coronary spasm, acute myocardial infarction, and/or stent thrombosis" will be referred to collectively as ACS for simplicity in this review.)

[a] DNH requested preliminary review of any identified Ferrlecit cases in advance of a labeling meeting that was scheduled for December 20, 2021, and a final review of the entire case series. DPV provided preliminary findings pertaining to Ferrlecit to DNH by email on December 13, 2021.

Documentation of the role of histamine and other inflammatory mediators in the pathophysiology of coronary artery spasm predated the eponym "Kounis Syndrome" (Felix et al. 1988; Pinto et al. 2019). Such events may have historically been referred to by other terms, such as allergic acute coronary syndrome, allergic angina (coined by Kounis before Kounis Syndrome), and allergic myocardial infarction (Roth and Cortes 2020; Nikolaidis et al. 2002; Pinto et al. 2019). The specific term "Kounis Syndrome" may not be widely recognized in the U.S. and has met some skepticism and outright criticism in the medical literature (Pinto et al. 2019, Witteles et al. 2016).

Diagnosis of Kounis Syndrome relies on clinical symptoms and signs as well as on laboratory and graphic evidence (Kounis 2016.) Clinical manifestations of Kounis Syndrome may include a mixture of signs and symptoms of a hypersensitivity reaction and ACS including (but not limited to): chest pain, dyspnea, nausea, vomiting, syncope, pruritis, urticaria, diaphoresis, pallor, palpitations, hypotension, and bradycardia. Kounis Syndrome generally occurs very rapidly after exposure to the antigen, and the majority of Kounis Syndrome cases (80%) tend to manifest within one hour after antigen exposure (Abdelghany et al. 2017).

Therapeutic implications for the concurrent allergic and coronary conditions of Kounis Syndrome involve the potential for worsening one condition while improving the other. Epinephrine is indicated for emergency treatment of allergic reactions including anaphylaxis. [b] However, epinephrine's chronotropic and inotropic effects (beta-1 receptor agonism) increase myocardial oxygen consumption which can worsen ACS, despite beneficial coronary vasodilation by beta-2 agonism (Kounis 2016; Manaker 2020; Campbell and Kelso 2021). Conversely, coronary vasospasm is generally treated with nitroglycerine or calcium channel blockers, but their vasodilatory effect can worsen anaphylaxis-associated hypotension (Slavich and Patel 2016). Additionally, opiates, which may be administered for severe chest pain in ACS, can induce release of inflammatory mediators from mast cells (Reeder et al. 2021; Kounis 2016; Blunk et al. 2004).

Kounis described three variants of Kounis Syndrome, and each is reflected in the case definition for this review (Kounis 2016; Cotter and Woronow 2020b). The three variants are based largely on the extent of a patient's pre-existing atherosclerotic disease when a hypersensitivity reaction triggers a mast cell-mediated inflammatory cascade that compromises the coronary circulation. [c]

- The Type I variant has normal, or nearly normal, coronary arteries and no predisposing factors for coronary artery disease. In this variant, acute release of inflammatory mediators may induce coronary artery spasm resulting in myocardial ischemia or infarction.
- The Type II variant has dormant pre-existing atherosclerotic disease. In this variant, acute release of inflammatory mediators may induce coronary artery spasm with normal

[b] EpiPen (epinephrine injection) labeling as of 12/24/2020, available from Drugs@FDA, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.

[c] The inflammatory cascade involves mast cell degranulation, initiated by an antigen-antibody interaction on the surface of mast cells and basophils or by activation of the complement system (Abdelghany et al. 2017). The most important inflammatory mediators include histamine, platelet activating factor, chemokines, chymase, tryptase, cathepsin-D, peptides, proteoglycans, cytokines, growth factors and arachidonic acid products (Kounis 2016).

cardiac enzymes and troponins, or coronary spasm together with plaque erosion or rupture, manifesting as acute myocardial infarction.

- The Type III variant experiences coronary artery stent thrombosis, and the occluding thrombus is found through histology to have been infiltrated by eosinophils or mast cells. This variant would also be diagnosed after sudden fatality if histology shows infiltration, by eosinophils or mast cells, of the coronary intima, media, or adventitia adjacent to the stent.

1.2 REGULATORY HISTORY

1.2.1 Labeling Decisions Following DPV Reviews of Kounis Syndrome

DPV has completed two reviews of Kounis Syndrome prompted by applicant CBE labeling supplements. DPV recommended objective description of the event but did not object to "Kounis Syndrome" placed in ADVERSE REACTIONS, Postmarketing Experience (AR PME) (Cotter and Woronow 2020b; Gish and Woronow 2020). A third recent DPV review identified cases of coronary artery vasospasm in the context of anaphylaxis but did not specifically attribute the events to Kounis Syndrome (Cotter and Woronow 2020a). Objections to using the eponym "Kounis Syndrome" in the label included concern that the eponym may not be widely embraced or understood among U.S. healthcare providers, that the term is not included in the 2020-ICD10-CM index, and that there is debate in the literature about whether the pathophysiology of Kounis Syndrome represents a distinct clinical entity (Cotter and Woronow 2020b; Gish and Woronow 2020; Debellas 2020; Davidson 2020; Voqui 2021). Eventual approved product labeling did not contain the eponym "Kounis Syndrome," but instead described the clinical event in AR PME as follows:

- *Acute myocardial ischemia with or without myocardial infarction may occur as part of an allergic reaction.* [d, e]
- *Anaphylaxis associated with [electrocardiogram] ECG ST segment changes (elevation or depression) consistent with myocardial ischemia or coronary spasm has also been reported.* [f]

1.2.2 IV Iron Product Approval Dates

FDA approval information for IV iron products is shown in Table 1.

Table 1: FDA Approval Information Among IV Iron Products

Product Name	FDA Application Number	Original Approval Date	Marketing Status	Applicant
INFeD (iron	NDA 017441	04/29/1974	Active	Allergan

[d] Unasyn (ampicillin/sulbactam) NDA 050608, Label for Action Date 10/09/2020, https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/050608s047lbl.pdf.
[e] Cefuroxime and dextrose in duplex container (cefuroxime sodium) NDA 050780, Label for Action Date 12/05/2020, https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/050780s020lbl.pdf.
[f] Bridion (sugammadex) NDA 022225, Label for Action Date 01/22/2021 SUPPL-7, https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022225s007s009lbl.pdf.

dextran)				
Dexferrum (iron dextran)	NDA 040024	02/23/1996	Discontinued	Luitpold
Proferdex (iron dextran)	NDA 017807	03/26/1981	Discontinued	New River
Ferrlecit (sodium ferric gluconate complex)	NDA 020955 ANDA 078215	02/18/1999 03/31/2011	Active Active	Sanofi Aventis West-Ward Pharms
Venofer (iron sucrose)	NDA 021135	11/06/2000	Active	Luitpold
Feraheme (ferumoxytol)	NDA 022180 ANDA 206604	06/30/2009 01/15/2021	Active Active	Amag Pharms Sandoz
Injectafer (ferric carboxymaltose)	NDA 203565	07/25/2013	Active	Luitpold
Monoferric (iron derisomaltose)	NDA 208171	01/16/2020	Active	Pharmacosmos

IV iron products are iron replacement products with indications summarized in Table 2.

Table 2. FDA Approved Indications Among IV Iron Products*

Product Name	Indication
INFed (iron dextran)	For treatment of adult and pediatric patients of age 4 months and older with documented iron deficiency who have intolerance to oral iron or an unsatisfactory response to oral iron.
Dexferrum (iron dextran)	For treatment of patients with documented iron deficiency in whom oral administration is unsatisfactory or impossible.
Ferrlecit (sodium ferric gluconate complex)	For treatment of iron deficiency anemia in adult patients and in pediatric patients age 6 years and older with chronic kidney disease receiving hemodialysis who are receiving supplemental epoetin therapy.
Venofer (iron sucrose)	For treatment of iron deficiency anemia in patients with chronic kidney disease.
Feraheme (ferumoxytol)	For the treatment of iron deficiency anemia in adult patients: • who have intolerance to oral iron or have had unsatisfactory response to oral iron, or • who have chronic kidney disease.
Injectafer (ferric carboxymaltose) Monoferric (ferric derisomaltose)	For the treatment of iron deficiency anemia in adult patients: • who have intolerance to oral iron or have had unsatisfactory response to oral iron, or • who have non-dialysis dependent chronic kidney disease.

* The indication for Proferdex (iron dextran) is not included in this table because an approved label was

not available on Drugs@FDA, nor was a label found in the DailyMed labeling archive as of October 13, 2021.

1.3 RELEVANT PRODUCT LABELING

1.3.1 Hypersensitivity Reactions

We inventoried current approved IV iron reference listed drug (RLD) labeling to understand whether, and to what extent, ACS is described within hypersensitivity reaction labeling of marketed IV iron products. [g] All the IV iron labels contained Hypersensitivity Reactions as the top item in WARNINGS AND PRECAUTIONS (W/P), with highly similar descriptions and instructions. Below is an example from the Venofer label:

> **5 WARNINGS AND PRECAUTIONS** [g]
> **5.1 Hypersensitivity Reactions**
> Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving Venofer. Patients may present with shock, clinically significant hypotension, loss of consciousness, and/or collapse. If hypersensitivity reactions or signs of intolerance occur during administration, stop Venofer immediately. Monitor patients for signs and symptoms of hypersensitivity during and after Venofer administration for at least 30 minutes and until clinically stable following completion of the infusion. Only administer Venofer when personnel and therapies are immediately available for the treatment of serious hypersensitivity reactions. Most reactions associated with intravenous iron preparations occur within 30 minutes of the completion of the infusion [see Adverse Reactions (6.1 and 6.2)].

Differences in the labeling of hypersensitivity reactions among the IV iron products include a BOXED WARNING in two product labels (INFeD and Feraheme), variations in recommended monitoring duration, and summaries of hypersensitivity reactions reported during clinical trials or postmarketing experience with the products.

Descriptions of ACS within summaries of hypersensitivity reactions include: [g]

- anaphylaxis, presenting with cardiac/cardiorespiratory arrest (Feraheme)
- dyspnea/chest pain (Ferrlecit)
- cardiovascular collapse (INFeD)

1.3.2 Acute Coronary Syndrome

We noted that all IV iron products are labeled for chest pain, chest discomfort, and/or chest tightness in ADVERSE REACTIONS (either from clinical trial experience [AR CTE] or postmarketing experience [AR PME]). [g] However, we acknowledge that chest pain, discomfort or tightness are non-specific for ACS. We also noted the following terms in Ferrlecit and Feraheme labeling: [g]

- Ferrlecit: angina pectoris, myocardial infarction (AR CTE)

[g] Citations for the IV iron products product labeling we referred to are provided in References, section 7.

- Feraheme: angina pectoris (AR CTE); ischemic myocardial events, cardiac/cardiorespiratory arrest (AR PME)
- INFeD: cardiac arrest (AR CTE/PME)

1.3.3 Hypotension

All IV iron product RLDs are labeled for hypotension, independent from hypersensitivity labeling, as shown in Table 3. [g]

Table 3. Labeling of Hypotension Across IV Iron Products

IV Iron	Label Section and Content Excerpt(s) *
Feraheme	W/P 5.2 Feraheme may cause clinically significant hypotension…
Venofer	W/P 5.2 Venofer may cause clinically significant hypotension…may be related to the rate of administration and/or total dose administered.
Ferrlecit	W/P 5.2 Ferrlecit may cause significant hypotension. Hypotension associated with lightheadedness, malaise, fatigue, weakness or severe pain in the chest, back, flanks, or groin has been reported. These hypotensive reactions may or may not be associated with signs and symptoms of hypersensitivity reactions and usually resolve within one to two hours…Ferrlecit may augment hypotension caused by dialysis… AR CTE hypotension (29%), syncope (6%), lightheadedness, vasodilation
INFeD	AR (CTE and PME are combined): hypotension, flushing (flushing and hypotension may occur from too rapid injections by the intravenous route), syncope
Injectafer	AR CTE: hypotension, AR PME: syncope
Monoferric	AR PME = hypotension, syncope

Abbreviations: IV= intravenous, W/P=Warnings and Precautions, AR=Adverse Reactions, CTE=Clinical Trial Experience, PME=Postmarketing Experience

1.3.4 Higher Incidence and/or Severity of Adverse Events with Doses Exceeding Recommended Amounts or Infusing Too Rapidly

Two IV iron product RLD labels describe impacts associated with above-recommended doses or infusion rates. [g]

Ferrlecit
AR PME: Individual doses exceeding 125 [milligram] mg may be associated with a higher incidence and/or severity of adverse events based on information from postmarketing spontaneous reports. These adverse events included hypotension, nausea, vomiting, abdominal pain, diarrhea, dizziness, dyspnea, urticaria, chest pain, paresthesia, and peripheral swelling.

Venofer

AR PME: Symptoms associated with Venofer total dosage or infusing too rapidly included hypotension, dyspnea, headache, vomiting, nausea, dizziness, joint aches, paresthesia, abdominal and muscle pain, edema, and cardiovascular collapse. These adverse reactions have occurred up to 30 minutes after the administration of Venofer injection. Reactions have occurred following the first dose or subsequent doses of Venofer. Symptoms may respond to intravenous fluids, hydrocortisone, and/or antihistamines. Slowing the infusion rate may alleviate symptoms.

1.3.5 Increased Risk of Toxicity in Patients with Underlying Conditions

In WARNING AND PRECAUTION 5.3, the INFeD product labeling states, "…Adverse reactions experienced following administration of INFeD may exacerbate cardiovascular complications in patients with pre-existing cardiovascular disease…" [g]

1.3.6 Proposed Labeling Change for Ferrlecit

Sanofi's CBE SUPPL-20 notified FDA that the following underlined text was added to the WARNINGS & PRECAUTIONS and ADVERSE REACTIONS sections of Ferrlecit labeling:

5 WARNINGS AND PRECAUTIONS [h]

5.1 Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving Ferrlecit in postmarketing experience. Patients may present with shock, clinically significant hypotension, loss of consciousness, or collapse. Monitor patients for signs and symptoms of hypersensitivity during and after Ferrlecit administration for at least 30 minutes and until clinically stable following completion of the infusion. Only administer Ferrlecit when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions *[see Adverse Reactions (6)]*.

Parenterally administered iron preparations can cause hypersensitivity reactions including serious and potentially fatal anaphylactic/anaphylactoid reactions. Hypersensitivity reactions have also been reported after previously uneventful doses of parenteral iron complexes.

Hypersensitivity reactions can also progress to Kounis Syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to iron-containing medicinal products for intravenous administration. In patients with present coronary disease or risks factors for coronary disease, Kounis Syndrome may be more severe. In those patients, iron-containing medicinal products for intravenous administration should be used only after careful risk/benefit evaluation.

In the single-dose, postmarketing, safety study one patient experienced a life-threatening hypersensitivity reaction (diaphoresis, nausea, vomiting, severe lower back pain, dyspnea, and wheezing for 20 minutes) following Ferrlecit administration. Among 1,097

[h] This version of the WARNINGS AND PRECAUTIONS 5.1 is public, updated June 30, 2021, and available on DailyMed: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1fe028ff-42ac-4329-b1a5-a9dadfcb79f6.

patients who received Ferrlecit in this study, there were nine patients (0.8%) who had an adverse reaction that, in the view of the investigator, precluded further Ferrlecit administration. These included one life-threatening reaction, six allergic reactions (including pruritus, facial flushing, chills, dyspnea/chest pain, and rash), and two other reactions (hypotension and nausea). Another two patients experienced (0.2%) allergic reactions not deemed to represent drug intolerance (nausea/malaise and nausea/dizziness) following Ferrlecit administration.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Cardiovascular System: hypotension (29%), hypertension (13%), syncope (6%), tachycardia (5%), bradycardia, vasodilatation, angina pectoris, myocardial infarction, pulmonary edema, Kounis Syndrome.

2 METHODS AND MATERIALS

DPV met with DNH on October 7, 2021 to discuss and agree on the methods applied in this review.

2.1 CASE DEFINITION

For this review, DPV adapted the tiered case definition developed for a prior review of Kounis Syndrome with Unasyn (ampicillin/sulbactam) (Cotter and Woronow 2020b). The Types I-III variants in the case definition correspond with the three variants of Kounis Syndrome (Kounis 2016). The case definition relies on imaging and laboratory findings (Tier A), or a combination of imaging or laboratory findings and clinical features (Tier B).

Case Definition Tier A

- **Type I Variant**
  - Imaging: normal or nearly normal coronary arteries without risk factors for coronary artery disease, AND
  - Laboratory: acute release of inflammatory mediators that may induce coronary artery spasm resulting in myocardial ischemia or infarction [i]

- **Type II Variant**
  - Imaging: culprit but quiescent preexisting atheromatous disease and coronary artery spasm, or coronary artery spasm together with plaque erosion or rupture, manifesting as acute myocardial infarction, AND [i]
  - Laboratory: acute release of inflammatory mediators that may induce either of above, and cardiac enzymes consistent with above

[i] Severe chest pain, usually at rest as well as with a concurrent ECG showing transient ST elevation, is the typical presentation of patients experiencing coronary artery spasm (CAS); and CAS typically responds to treatment with nitroglycerin or calcium-channel blockers (Pendela et al. 2020; Kondo and Terada 2017).

- **Type III Variant**
  - Imaging: coronary artery stent thrombosis, AND
  - Laboratory: aspirated thrombus specimens stained with hematoxylin-eosin and Giemsa demonstrate the presence of eosinophils and mast cells, respectively

  (This variant is also diagnosed in patients with stent implantation who died suddenly and histological examination of coronary intima or media and/or adventitia adjacent to stent is infiltrated by eosinophils and/or mast cells.)

Case Definition Tier B

- Case reports imaging findings, but only clinical features strongly compatible with laboratory features as defined in Tier A.

  OR
- Case reports laboratory findings, but only clinical features strongly compatible with imaging features as defined in Tier A.

2.2 CAUSALITY CRITERIA

After applying the case definition, we evaluated cases for a causal relationship utilizing the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) Causality Assessment System shown in Table 4. Causality assessment was performed independently by two reviewers, and differences in assessments were discussed.

Table 4. WHO-UMC Causality Assessment System (Uppsala 2018)

Causality Term	Assessment Criteria*
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations

Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified
* All points should be reasonably complied with.	

2.3 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 5.

Table 5. FAERS Search Strategy*	
Date of search	October 4, 2021
Time period of search	All dates through October 3, 2021
Search type	Drug Safety Analytics Dashboard (DSAD) Quick Search
Product terms	Product Active Ingredient: Iron dextran; iron sucrose; ferric carboxymaltose; ferric derisomaltose; sodium ferric gluconate complex; ferumoxytol; ferumoxytol non-stoichiometric magnetite
MedDRA search terms (Version 24.0)	SMQ - *Ischaemic heart disease* (narrow search) PT - *Vascular stent thrombosis*
* See Appendix A for a description of the FAERS database. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, SMQ=Standardised MedDRA Query, PT=Preferred Term	

2.4 LITERATURE SEARCH STRATEGY

DPV searched the medical literature with the strategy described in Table 6. A broader search was performed in PubMed and a narrower search in Embase, consistent with the approach taken in previous DPV reviews of Kounis Syndrome.

Table 6. Literature Search Strategy		
Date of search	September 20, 2021	October 4, 2021
Database	Embase	PubMed

Table 6. Literature Search Strategy		
Search terms	'DRUG' AND [humans]/lim AND [english]/lim AND 'Kounis Syndrome' *	(iron sucrose OR iron dextran OR ferric carboxymaltose OR ferric derisomaltose OR sodium ferric gluconate OR ferumoxytol OR ferric compounds) AND (Kounis Syndrome OR allergic angina OR allergic vasospastic angina OR allergic acute coronary syndrome OR prinzmetal angina OR variant angina OR (myocardial ischemia AND hypersensitivity))
Years included in search	All	All
Other criteria		Humans
* The active ingredient was entered for DRUG except where Embase suggested a different term: ferric gluconate for sodium ferric gluconate complex; iron saccharate for iron sucrose; and iron isomaltose for iron derisomaltose.		

2.5 FDALABEL DATABASE SEARCH STRATEGY

DPV searched the FDALabel database for labels containing the term Kounis Syndrome as described in Table 7. The data in FDALabel is sourced from DailyMed's Structured Product Labeling (SPL) archive, which stores labeling submitted by companies (CDER OTS 2020).

Table 7. FDALabel Database Search Strategy for Kounis Syndrome in All Drug Products	
Date of search	September 30, 2021
Labeling types	Human Prescription Drug and Biological Products – PLR Format Human Prescription Drug and Biological Products – Non-PLR Format
Application types	ANDA, BLA, NDA
Product name	All products
Labeling Full Text Search	'Kounis Syndrome'
FDALabel, http://fdalabel.fda.gov/fdalabel-r/ui/search Abbreviations: PLR=Physician Labeling Rule	

2.6 APPLICANT ASSESSMENT AND PERIODIC SAFETY REPORTS

2.6.1 Sanofi Safety Evaluation Report

Sanofi submitted a Safety Evaluation Report (SER) to DNH with the CBE NDA labeling supplement to support labeling changes described in Section 1.3.6. The objective of the SER was to assess if a causal relationship exists between Ferrlecit use and the occurrence of Kounis Syndrome (Rakshita 2021). DPV read the SER to:

- understand Sanofi's approach to assessing Kounis Syndrome with Ferrlecit use and IV iron use;

- understand how Sanofi reached the conclusion that the weighted cumulative evidence is sufficient to support a causal association between Ferrlecit and Kounis Syndrome;
- understand how Sanofi's conclusion in the SER may relate to the proposed Ferrlecit labeling changes; and
- provide our overall assessment of Sanofi's approach.

DPV also referenced Sanofi's most recent periodic safety report (PSR) for Ferrlecit use estimations (Sanofi 2021b).

2.6.2 Periodic Safety Reports

DPV screened the most recent PSRs from the other NDA holders of IV iron products to identify applicants that are assessing Kounis Syndrome with IV iron use, and for product use estimates. [j] If product use estimates were not provided in the PSRs, we referred to distribution data provided from the applicant in its most recent annual report.

- INFeD (iron dextran) NDA 017441 Periodic Adverse Drug Experience Report (PADER), October 11, 2020 – October 10, 2021 (Allergan 2021a)
- Venofer (iron sucrose) NDA 021135 PADER, November 7, 2020 – November 6, 2021 (American Regent 2021b)
- Feraheme (ferumoxytol) NDA 022180 Periodic Safety Update Report (PSUR), July 1, 2020 – June 30, 2021 (Covis 2021)
- Injectafer (ferric carboxymaltose) NDA 203565 PADER, July 26, 2020 – July 25, 2021 (American Regent 2021c)
- Monoferric (ferric derisomaltose) NDA 208171 PADER, July 16, 2021 – October 15, 2021 (Pharmacosmos 2021)

3 RESULTS

3.1 FAERS CASE SELECTION

The FAERS search retrieved 174 reports. After applying the case definition in Section 2.1 and accounting for duplicate reports, four cases were included in the case series of Kounis Syndrome reported with IV iron use (see Figure 1). Two of the four cases were also literature reports (Ahluwalia et al. 2004; Hao et al. 2014).

Figure 1. FAERS Case Selection

[j] We did not screen periodic safety reports for Proferdex (iron dextran) NDA 017807 and Dexferrum (iron dextran) NDA 040024 because both products are discontinued (American Regent 2021d; Shire 2019).

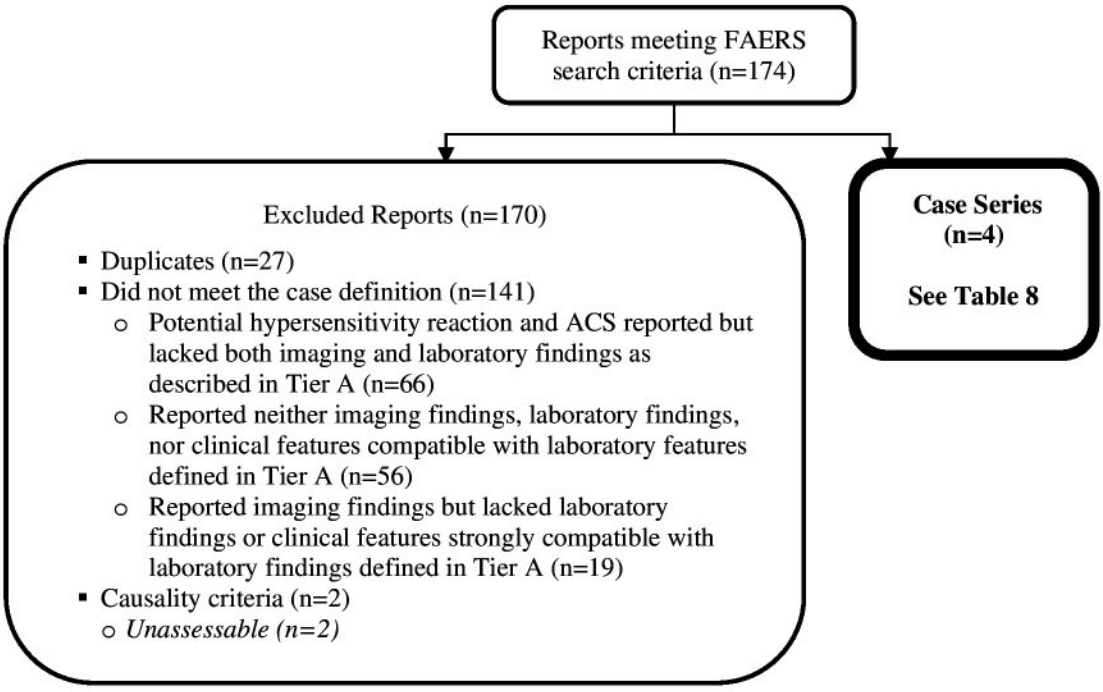

Table 8 summarizes the four FAERS cases of Kounis Syndrome reported with IV iron products for this case series.

Appendix B contains a line listing of the four cases in this case series.

Appendix C contains clinical case details for each of the four cases in this case series.

Table 8. Descriptive Characteristics of Kounis Syndrome with IV Iron Products in this FAERS Case Series, Received by FDA Through October 3, 2021

(N=4) *

Age (years) (n=4)	Median Mean Range	60 56.75 37-70
Sex	Male Female	2 2
Country	United States Canada China	2 1 1
Kounis variant/ Evidence tier	Type I/Tier B Type II/Tier B Type III/Tier B	2 1 1
Report type	Expedited Direct	3 1

Table 8. Descriptive Characteristics of Kounis Syndrome with IV Iron Products in this FAERS Case Series, Received by FDA Through October 3, 2021 (N=4) *		
IV iron	Ferumoxytol Iron dextran Iron sucrose SFGC	1 1 1 1
Initial FDA received year	2009 2013 2014 2015	1 1 1 1
Serious outcome(s) (n=4) †	DE LT HO OT	1‡ 3 3 2
Clinical outcome	Recovered Death	3 1 ‡
Causality assessment	Probable Possible	1 3

* Includes any case identified in either FAERS alone or in both FAERS and the literature

† Reports with at least one serious outcome. A report can have one or more serious outcome. For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events. A case can have more than one serious outcome.

‡ The case with fatal outcome is summarized in Appendix C (FAERS ID 9670358).

Abbreviations: IV-intravenous, DE=Death, HO=hospitalization, LT=life-threatening, OT=other serious important medical event(s), SFGC=sodium ferric gluconate complex (Ferrlecit)

While all four cases in the series provided elements sufficient for inclusion under Tier B of the case definition, none provided Tier A evidence of Kounis Syndrome following exposure to IV iron products. We highlight two cases below: one is the only case assessed as "probable" using the WHO-UMC causality assessment system and the other is the only case identifying Ferrlecit (selected considering the proposed Ferrlecit labeling changes described in Section 1.3.6). Key portions of the narrative used to justify the case selection, and other noteworthy details, are underlined in the text below.

- **FAERS Case # 10238870, iron sucrose, China, Expedited, Literature report (Hao Z et al. 2014: "Kounis Syndrome Induced by Iron Sucrose"), 2014, Serious outcomes: hospitalization, life-threatening**

A 57-year-old man with iron-deficiency anemia (supporting labs not reported) was prescribed IV iron sucrose as an outpatient. No other concurrent medications were reported, and no additional medical history was provided other than "no previous history of hypertension." During the first iron sucrose infusion, the patient complained of dyspnea, malaise, and sweating (treatment for these symptoms was not reported). The same symptoms reoccurred upon receiving his second dose, but the dyspnea was more severe and his condition "quickly deteriorated" with continuous

coughing, pink frothy sputum, hypotension (60/40 mmHg), and tachycardia (140 bpm). He was admitted to the hospital, administered dopamine and norepinephrine, and his vital signs were as follows: pulse rate approximately 96 bpm; blood pressure of 60/40 mmHg; and oxygen saturation ("SaO_2") 70-75% suggesting "severe hypoxemia." Cardiac troponin I levels were elevated "above 50 µg/L" (exact level not reported [NR]; reference range 0-0.15 µg/L). Electrocardiogram (ECG) showed ST-segment elevation in leads I and aVL and demonstrated "slightly impaired left lateral ventricular contraction and no mechanical complications." Computed tomography (CT) revealed acute pulmonary edema and effusion. The patient was diagnosed with acute ST-segment elevation myocardial infarction (STEMI) and cardiogenic shock. Coronary angiography revealed a 70-80% diffuse lesion in the mid-distal end of the left circumflex artery (LCx) with TIMI grade 3 flow "which corresponded to the lateral wall infarction indicated by ECG [electrocardiogram] and echocardiogram;" no lesions were found in the left main coronary artery (LMCA), right coronary artery, or left anterior descending (LAD) artery. [k] Ventriculography showed "essentially normal findings apart from slightly impaired interior wall contraction." Swan-Ganz catheterization revealed "normal systemic vascular resistance index" (2345 dyne s-1 centimeter (cm) 5 meter $(m)^2$) with "relatively normal heart function" (cardiac output 4.5 liter (L)/minute (min); cardiac index 2.4 $L/min/m^2$) under the administration of dopamine and norepinephrine. Following rehydration and treatment with an unspecified vasoactive agent, the patient's condition stabilized, and ECG showed ST-segment regression on hospital admission day 2. The reporters retrospectively suspected that anaphylactic shock had triggered the STEMI because: hypoxemia and hypotension without severe stenotic lesion in the LMCA or LAD, no mechanical complications or pericardial tamponade rendered it unlikely that STEMI had triggered shock; hypovolemia and vasodilation (decreased systemic vascular resistance in the absence of norepinephrine), fluid redistribution, and relatively reserved cardiac output supported STEMI secondary to anaphylactic shock. Circulating IgE levels were within normal limits when tested on day 8 of hospitalization, at 56.42 international units (IU)/milliliter (mL) (reference range 1.27-241.3 IU/mL). Chest CT showed decreased pulmonary exudation on admission day 14. No lesions were found upon repeat coronary angiography on admission day 24, and the diffuse lesion previously noted in the LCx had disappeared. The patient was discharged on admission day 25.

Reviewer Comments: Iron sucrose administration was temporally associated with the events described in this case. The patient received two infusions of iron sucrose with symptoms during each and more severe during the second. The time between infusions was one day. The patient experienced the elements necessary for the Tier B, Type I variant of the case definition: the imaging with near normal coronary artery status and no reported cardiac disease risk factors meet Type I criteria; the imaging without laboratory inflammatory markers meet Tier B criteria. The coronary angiography identified an isolated 70 – 80% lesion in the LCx but otherwise normal coronary arteries. The lesion was described as transient and attributed to vasospasm. There was no mention of any underlying coronary lesion or any procedural intervention. Management as described included volume resuscitation and an unspecified vasoactive agent

[k] A >40 to <80% diameter narrowing noted during coronary angiography is considered a stenosis of intermediate severity (Kern 2020). According to the Thrombosis in Myocardial Infarction (TIMI) flow grading system, grade 3 flow corresponds with full perfusion (more than 90%) of the infarct vessel with normal flow (Gibson et al. 2020).

which may have been a pressor or may have been medication to reduce coronary vasospasm.[1] *Due to lack of correlation between the critical nature of the patient's condition and the isolated coronary artery findings during the patient's deterioration, an alternate etiology of shock was considered. Anaphylaxis was diagnosed retrospectively. However, the detailed cardiac information and monitoring provided are reasonably consistent with anaphylaxis as are the clinical symptoms, including worsening on second exposure to infusion of the iron sucrose. No specific treatment for anaphylaxis was given, likely due to the delay.*
Causality: Probable

- **FAERS Case # 11228784, sodium ferric gluconate complex (Ferrlecit), USA, Direct Report, 2015, Serious outcomes: life-threatening, other medically significant**

A 63-year-old woman was administered 250mg Ferrlecit IV over two hours for microcytic anemia with iron deficiency (iron saturation 3%, ferritin 21, reference ranges [RR] not provided) secondary to blood loss during hospitalization (the reason for hospitalization was not reported). Her past medical history included coronary artery disease (CAD) with three stents (not reported whether the stents were bare metal or drug-eluting), hypertension, hyperlipidemia, peripheral artery disease, depression, tobacco use, and she had a history of gastrointestinal bleeding. Her reported allergies were penicillin (swelling), strawberries (swelling). Reported concomitant medications were aspirin, clopidogrel, metoprolol tartrate, lisinopril, atorvastatin, pantoprazole, venlafaxine, lamotrigine, baclofen, and furosemide. Approximately 1.5 hours into the Ferrlecit infusion, she developed hives and itching and was treated with diphenhydramine and famotidine. She then became hypotensive and diaphoretic with cool extremities. IV fluids were administered with stabilization of systolic blood pressure in the 80's. An EKG revealed ST segment elevations (leads not reported). Left heart catheterization revealed in-stent thrombosis and the patient received a drug-eluting stent to the LAD artery. Laboratory data was reported for the day after the Ferrlecit infusion: hemoglobin (Hgb) 6.8; hematocrit (Hct) 25.7; mean corpuscular volume (MCV) 67; mean corpuscular hemoglobin (MCH) 18; mean corpuscular hemoglobin concentration (MCHC) 26 (RR not provided). The patient had no further events.

Reviewer Comments: Given the incomplete information and potential alternate explanations for the patient's in-stent thrombosis, this case represents weak evidence to support a causal association between Ferrlecit and the observed cardiac event. Although we deemed causality as "possible" for reasons discussed below, we also considered a causality assessment of "unassessable" due to the missing clinical details.

Ferrlecit administration was temporally associated with the events described in this case. The patient experienced the elements necessary for the Tier B, Type III variant of the case definition. Coronary angiography showing stent thrombosis closely following Ferrlecit administration provides imaging evidence of the coronary event and is generally supported by the observed ST-segment elevations (Cutlip and Abbott 2020). Hives and itching are consistent with clinical manifestations of a hypersensitivity reaction involving activation of mast cells and histamine release, but criteria for Tier A were not met without laboratory evidence of presence of eosinophils and mast cells in aspirated thrombus specimens. The hypotension observed after diphenhydramine and famotidine administration should be assessed with caution. Hypotension

[1] nitroglycerine or calcium channel blockers

accompanied by cool extremities as described in this case is consistent with a cardiac origin versus a hypersensitivity origin (Sharma et al. 2021). However, hypotension is independently associated with diphenhydramine and with Ferrlecit (Micromedex 2021). [g] *Moreover, Ferrlecit use in this patient was off-label and the dose was double what is recommended in labeling (125mg); Ferrlecit doses exceeding 125mg may be associated with a higher incidence and/or severity of adverse events.* [g] *Additionally, the patient's prominent history of CAD with multiple prior stents, and other risk factors described in the case (e.g., tobacco use, left anterior descending artery lesion, potential in-stent restenosis), may provide one or more possible alternative etiologies for stent thrombosis (Cutlip and Abbott 2020). Stent thrombosis attributed to something other than inflammatory mediators secondary to a hypersensitivity reaction would not appear to fit the definition of Kounis Syndrome. Further, the concept that in-stent thrombosis could result from anaphylactoid processes requires further investigation (Pinto et al. 2019). So, while a causal association between Ferrlecit and the hypersensitivity reaction described in this case seems likely, a causal association between the hypersensitivity reaction and subsequent in-stent thrombosis is less clear but possible among other possible etiologies. Several factors limited our ability to consider other potential etiologies or contributing factors while assessing this case, including lack of reported: reason for the patient's hospitalization; time since prior stent placement and stent type; clarification of current smoking status; whether dual antiplatelet therapy was continued during the hospitalization; and status of other risk factors for stent thrombosis.*
Causality: Possible

3.2 LITERATURE SEARCH

We did not identify additional literature cases of Kounis Syndrome associated with IV iron products. Two published case reports were identified that were not found by the FAERS search, but both were excluded because they did not meet the DPV case definition for Kounis Syndrome (Mishra et al. 2013; Fiechter et al. 2005).[m] Neither reported imaging and/or laboratory findings as described in the DPV case definition, so they did not meet either tier of the case definition. Further, Fiechter et al. described myocardial infarction before IV iron administration.

3.3 FDALABEL SEARCH

We identified one label with the term 'Kounis Syndrome' in the FDALabel database, and it was the label for Ferrlecit, NDA 020955. Therefore, Ferrlecit appears to be the only drug product with the term 'Kounis Syndrome' in its labeling. (A relevant excerpt of the Ferrlecit labeling was shown in Section 1.3.3.)

3.4 APPLICANT ASSESSMENT AND PERIODIC SAFETY REPORTS

3.4.1 Sanofi Safety Evaluation Report

[m] The literature search identified a Letter to the Editor by Soufras, Kounis, and Kounis 2013 that was asking whether a published case report by Mishra et al. 2013 could have been Kounis Syndrome rather than an anaphylactic reaction alone.

At the end of its SER, Sanofi concluded: "Based on review of the Sanofi GPV database, worldwide scientific literature, main reference textbooks, comparator labels and external databases, the weighted cumulative evidence is ***sufficient*** to support a causal association between Kounis Syndrome and [sodium ferric gluconate complex] SFGC."

Sanofi's search of its global pharmacovigilance (GPV) database is described in Table 9.

Table 9. Sanofi Global Pharmacovigilance Database Search Strategy	
Drug terms	Sodium ferric gluconate complex (SFGC)
Search terms MedDRA 23.1	*Ischaemic heart disease* SMQ broad
Years included in search	All reports until February 1, 2021
Additional criteria	all solicited and unsolicited cases, medically confirmed and non-medically confirmed, including diagnosis and symptoms

Sanofi provided a case definition it used to identify a case series for its review. Note that it allowed for inclusion of cardiac events not associated with hypersensitivity reactions:

> "Sentinel case definition: All well documented cases that reported with Kounis Syndrome/ coronary arteriospasm/ MI [myocardial infarction] following therapy with SFGC in the presence of a plausible time-to-onset (TTO), diagnostic confirmation (electrocardiogram [ECG] or coronary angiography and laboratory confirmation for elevation of serum histamine, tryptase, troponin I) with/ without positive dechallenge and/ or rechallenge were considered sentinel."

Sanofi's search of scientific literature is described in Table 10.

Table 10. Sanofi Literature Search Strategy	
Databases	Medline, Embase
Search description	"articles reporting or discussing SFGC and Kounis Syndrome"
Years included in search	1974 to February 9, 2021*
* The literature search was conducted on February 9, 2021. Abbreviations: SFGC=Sodium ferric gluconate complex (Ferrlecit)	

Sanofi's research of reference texts, comparator labels, and external databases is summarized in Table 11.

Table 11. Sanofi Findings from Review of Reference Texts, Comparator Labels, and External Databases	
Reference texts	Micromedex mentions the occurrence of chest pain and myocardial infarction with SFGC. Martindale mentions the occurrence of ischemic heart disease and coronary artery disease with SFGC.
Comparator labels (SmPCs)	Warnings and Precautions: Each referenced comparator label included, "there have been reports

	of hypersensitivity reactions which progressed to Kounis Syndrome (acute allergic coronary arteriospasm that can result in MI…" Adverse reactions: Comparator labels included "Kounis Syndrome" as well as "chest pain."
External databases	FAERS: No case reports of Kounis Syndrome or coronary ateriospasm reported with SFGC. Found 20 events belonging to narrow SMQ *Ischaemic heart disease*, and of those, Sanofi found the PTs *Acute myocardial infarction* and *Coronary artery dissection* to indicate an SDR. EVDAS: Found 19 relevant PTs; however, none of the reported PTs met preset criteria for SDR.
Abbreviations: EVDAS=EudraVigilance Data Analysis System; SDR=signal of disproportionate reporting; SFGC=Sodium ferric gluconate complex (Ferrlecit); SmPC=Summary of Product Characteristics	

Sanofi identified 14 "relevant" cases by employing the search strategy described in Table 9; however, eight cases met the sentinel case definition due to the presence of a highly suggestive time-to-onset, and only three of eight reported cardiovascular adverse events secondary to hypersensitivity/anaphylactic reactions. The remaining five sentinel cases reported cardiac events with no associated hypersensitivity/anaphylactic reactions; thus, they do not appear to be consistent with Kounis Syndrome.

Sanofi identified three published case reports of Kounis Syndrome and IV iron preparations with the literature search strategy described in Table 10. [n] Sanofi noted that none of the publications described Kounis Syndrome following Ferrlecit therapy.

Table 12 summarizes the three sentinel cases, after excluding the five cases identified by Sanofi that reported "cardiac events with no associated hypersensitivity/ anaphylactic reactions," from Sanofi's GPV database, and three literature case reports identified and assessed by Sanofi, for a total of 6 cases. [n]

[n] The Sanofi SER identified four literature publications; however, one publication appears to have been included erroneously. The SER stated that the patient received iron dextran; however, the referenced publication states the patient received low-molecular-weight dextran (Dextran 40) (Akita et al. 2015).

Table 12. Sentinel and Literature Cases Identified by Sanofi * (N=6) *					
Sanofi Case # or Authors/ Demography	**IV Iron**	**Preferred Term(s) or Events**	**TTO/ Dechallenge/ Rechallenge/ Outcome**	**Risk Factors/ Confounding Factors Identified by Sanofi**	**DPV Reviewer Comments**
Sentinel cases with cardiac events secondary to hypersensitivity/anaphylactic reactions. (n=3)					
DE01-03376/ Female	SFGC	Cardiac arrest	2 minutes/ NA/NA/ Recovered		*Does not meet DPV CD given limited information provided. Corresponding FAERS report not found.* †
200216476G DDC/ 66-yo female	SFGC	MI, blood CPK increased, myocardial necrosis marker increased	1.5 hours/ NA/NA/ Fatal	PE induced MI. Hemodialysis = increased risk of developing PE.	*Does not meet DPV CD – lacked imaging and lab findings described in CD. FAERS ID 3873060, found in DPV search. Autopsy: cause of death PE resulting in MI and GI bleed; not consistent with Kounis Syndrome etiology.*
2014SA148726/ 79-yo female	SFGC	Acute MI	Same day/ NA/NA/ Fatal	Hx of cardiac failure and HTN precluded definite causality.	*Does not meet DPV CD – lacked imaging and lab findings described in CD. FAERS ID 10570782, found in DPV search.*
Identified by Sanofi as a published case report of Kounis Syndrome. (n=3)					
Soufras GD et al. 2013/ 20-yo female	Iron sucrose	Anaphylactic shock, cardiac arrest	"following infusion"/ NA/NA/ Fatal		*Does not meet DPV CD – lacked imaging and lab findings described in CD.* ‡
Zhan G et al. 2014 (Hao et al. 2014)/ 57-yo gender NR §	Iron sucrose	Hypotension, tachycardia, hypoxemia, elevated troponin I, STEMI, cardiogenic shock, anaphylaxis, Kounis Syndrome	"following second iron sucrose admini-stration"/ NA/NA/ Recovered		*Met DPV CD and is in case series. FAERS ID 10238870.*

Table 12. Sentinel and Literature Cases Identified by Sanofi * (N=6) *					
Sanofi Case # or Authors/ Demography	**IV Iron**	**Preferred Term(s) or Events**	**TTO/ Dechallenge/ Rechallenge/ Outcome**	**Risk Factors/ Confounding Factors Identified by Sanofi**	**DPV Reviewer Comments**
Ahluwalia MS et al. 2004/ 37-yo female	Iron dextran	Anaphylactic-type reaction, severe chest pain, dyspnea, elevated troponin, mild left ventricular systolic function with EF 45%, non-STEMI	"immediately after the infusion"/ NA/NA/ Recovery		*Met DPV CD and is in case series. FAERS IDs 6920633, 5793538, 7242745.*
Kawata T et al. 2015 (Akita et al. 2015)/ 70-yo male ‖	Patient did not receive an IV iron; low-molecular weight dextran appears to have been erroneously called iron dextran. ¶				

* Excerpted from SER sections 3.3.2.1, 3.4, and 4.
† We were unable to definitively identify this report in FAERS despite reading all reports of the PT *Cardiac arrest* with SFGC; the Sanofi case number did not match any of the manufacturer control numbers, and none reported a time-to-onset of two minutes.
‡ The literature search identified a Letter to the Editor by Soufras, Kounis, and Kounis 2013 that was asking whether a published case report by Mishra et al. 2013 could have been Kounis Syndrome rather than an anaphylactic reaction alone.
§ The SER in-text citation was "Zhan G et al (2014);" however, Zhan G is the fourth author listed. Therefore, our in-text citation of the publication is, Hao et al 2014.
‖ The SER in-text citation was "Kawata AT et al. (2015);" however, this appears to be a conflation of the names of the first two authors of the publication, Tomomi Akita and Masahito Kawata. Therefore, our in-text citation of the publication is, Akita et al. 2015.
¶ The SER stated that the patient identified by Akita et al. received iron dextran; however, the referenced publication states the patient received low-molecular-weight dextran (Dextran 40) (Akita et al. 2015).
Abbreviations: ACS=acute coronary, CD=case definition, CPK=creatine phosphokinase, DM=diabetes mellitus, EF=ejection fraction, GPV=global pharmacovigilance, HTN=hypertension, Hx=history, IV=intravenous, MI=myocardial infarction, NA=not applicable, NR=not reported, PE=pulmonary embolism, PT=Preferred Term, SFGC=sodium ferric gluconate complex (Ferrlecit), STEMI=ST segment elevation myocardial infarction, TTO=time-to-onset, yo=year-old

Reviewer comments: We did not identify any additional cases from Sanofi's SER.

We identified limitations in Sanofi's SER that are important to consider when interpreting the results of its analysis. Kounis Syndrome is comprised of a hypersensitivity reaction and ACS (Kounis 2016). However, Sanofi's sentinel case definition allowed for inclusion of "cardiac events with no associated hypersensitivity/anaphylactic reactions." Reports apparently lacking the key hypersensitivity component do not appear to support a signal for Kounis Syndrome. A rigorous case definition and a rigorous application of the case definition, therefore, is important and justified to identify cases of Kounis Syndrome.

In addition, one of the publications identified by Sanofi should not be interpreted as a case because the product was incorrectly reported as iron dextran when, in fact, the patient was administered low-molecular-weight dextran (Akita et al. 2015). [n] *Thus, Sanofi identified three sentinel cases with Ferrlecit (out of 14 reports from its GPV database) plus three published case reports involving iron sucrose or iron dextran, for a total of six cases that may be consistent with Kounis Syndrome.*

In addition to limitations cited above, DPV's more rigorous case definition combined with DPV's narrower FAERS search strategy led to very little overlap between the case series. DPV's FAERS and literature searches identified all three applicable published case reports summarized in the SER; however, only two met the DPV case definition (Ahluwalia et al. 2004; Hao Z et al 2014). Additionally, DPV's case series does not include the reports Sanofi identified from its GPV database; however, we identified one case involving Ferrlecit that was not identified by Sanofi because it was a direct report to FAERS (FAERS ID # 11228784), and additional cases involving other IV iron products. Despite these differences in approach and resulting case series, we do not intend to dispute Sanofi's overall conclusion in the SER. However, see Sections 4-6 for discussion of Sanofi's proposed Ferrlecit labeling revisions.

3.4.2 Periodic Safety Reports

One PSR screened by DPV included an assessment of an IV iron product and Kounis Syndrome. The Applicant's conclusions regarding Kounis Syndrome with its IV iron product are summarized below.

- Injectafer (ferric carboxymaltose) NDA 203565 (American Regent 2021c) – The Applicant identified one report with the PTs *Kounis Syndrome* and *Acute coronary syndrome* (Applicant case # 2021000331) regarding a 65-year-old male patient who experienced retrosternal pain, profuse sweating, and asthenia during his second infusion (a 500mg bolus) of ferric carboxymaltose. The Applicant made only brief comments about the case: "Confounding factors included this patient's medical history of arterial hypertension and dyslipidaemia as well as concomitant medications of ramipril (Triatec) and atorvastatin calcium (Torvast). Reportedly, this patient recovered from the event although remedial treatment was unspecified."

Reviewer comments: This report was also found by our search (corresponding FAERS ID 18864189). The report described imaging findings of normal coronary arteries; however, it did not meet the DPV case definition because it did not provide laboratory evidence or clinical features strongly compatible with laboratory evidence defined in Tier A of the DPV case definition.

The remaining PSRs screened by DPV did not include an assessment of the applicants' IV iron product and Kounis Syndrome.

Product use estimations provided by each applicant are summarized in Table 13.

Table 13. Intravenous Iron Product Use Estimates

Product Name	**Reported Sales or Exposure Estimate from Marketing** (one-year reporting period)
INFeD (iron dextran) (Allergan 2021b)	(b)(4) vials distributed domestically*
Ferrlecit (sodium ferric gluconate complex) (Sanofi 2021b)	(b)(4) (domestic and foreign markets combined)
Venofer (iron sucrose) (Vifor 2021a)	(b)(4) defined daily doses (or (b)(4) patient years) (domestic and foreign markets combined)
Feraheme (ferumoxytol) (Covis 2021)	(b)(4) doses distributed domestically †
Injectafer (ferric carboxymaltose) (Vifor 2021b)	(b)(4) defined daily doses (or (b)(4) patient years) (domestic and foreign combined)
Monoferric (iron derisomaltose) (Parexel 2021)	(b)(4) packages distributed (domestic and foreign markets combined) ‡

* There is no distribution of InFed to foreign markets (Allergan 2021b).
† Feraheme was not marketed in foreign markets during the reporting period (Covis 2021).
‡ Monoferric NDA 208171 was approved January 16, 2020, but the product was not commercially launched in the U.S. until October 1, 2020; therefore, the reported total represents (b)(4) packages distributed in the U.S. from 10/1/2020-1/15/2021 and (b)(4) packages distributed in foreign markets from 1/1/2020-12/31/2020 (Parexel 2021).

Reviewer comments: The exposure and distribution data provided in Table 13 indicate wide use of IV iron products domestically and abroad (where applicable).

4 DISCUSSION

The main challenge of this review was to identify and assess postmarketing cases displaying evidence of a specific pathological mechanism - Kounis Syndrome – wherein a hypersensitivity reaction to a drug (e.g., IV iron products) causes acute inflammatory mediator release resulting in coronary artery vasospasm or plaque rupture with or without myocardial infarction or stent thrombosis. The DPV case definition, in accordance with Kounis' description of three Kounis Syndrome variants, aimed to find evidence of this mechanism in postmarketing reports. Evidence

is important because there are other known mechanisms for ACS associated with IV iron products including acute hypotension (associated with a hypersensitivity reaction, high dose or infusion rate, use of diphenhydramine, and/or use of epinephrine when a rate-related infusion reaction is misinterpreted as an allergic reaction) and severe anemia (Thygesen et al. 2018; Auerbach 2021).

Overall, our case series provides only limited support of the specific pathological mechanism described by Dr. Kounis as Kounis Syndrome. DPV found a possible causal association between IV iron products and Kounis Syndrome based on four cases from FAERS that met our tiered case definition for Kounis Syndrome. All four cases provided elements necessary for "Tier B" classification and none provided the level of evidence necessary for "Tier A" classification. We assessed the causal relationship as probable for one case, and possible for the remaining three cases using the WHO-UMC Causality Assessment System. The case assessed as probable provided imaging findings and clinical features consistent with a transient coronary artery vasospasm in close temporal association with an IV iron product, consistent with the Kounis syndrome mechanism for a Type I variant, although anaphylaxis was diagnosed in retrospect and weakly supported (Hao et al. 2014). We did not identify additional cases from the medical literature, nor from the Sanofi SER. However, two of the literature cases summarized by Sanofi involving other IV iron products were also reported to FAERS, met the DPV case definition, and were thus included in our case series.

Hypersensitivity reactions are associated with IV iron use and prominently labeled across the drug class, providing biologic plausibility for IV iron use to initiate the release of acute inflammatory mediators from mast cells which could then trigger coronary artery vasospasm and/or plaque rupture manifesting in ACS (Kounis Syndrome). Biologic plausibility and close temporal relationship between IV iron use and the subsequent events may provide evidence of a causal association between an IV iron and Kounis Syndrome. However, the two components that comprise a case of Kounis Syndrome present an interesting challenge for causality assessment because both events (hypersensitivity reaction and ACS) must be considered, as must the link between the two.

Assessing causal factors in the hypersensitivity reaction component of Kounis Syndrome may be less complicated than the subsequent ACS event, particularly given other mechanisms for ACS with IV iron products mentioned above, and particularly in patients with pre-existing coronary disease or other risk factors for ACS. An example is the Ferrlecit case we identified which described risk factors that could independently trigger stent thrombosis regardless of the concurrent hypersensitivity reaction, and the case did not provide laboratory evidence of eosinophils and mast cells in the thrombus specimen that otherwise may have more strongly supported Kounis Syndrome pathophysiology (making it a Tier B case). Further, the concept that in-stent thrombosis could result from anaphylactoid processes requires further investigation (Pinto et al. 2019). Thus, Kounis Syndrome was one theoretical explanation among other plausible explanations for the described stent thrombosis or may have been one of many contributing factors that culminated in stent thrombosis. We also identified other plausible explanations and/or contributing factors when assessing the remaining two cases with possible causality in our case series.

While we believe the case series does little to corroborate an association between the specific mechanism of Kounis Syndrome and IV iron products, the cases do describe events associated with acute myocardial ischemia in the context of hypersensitivity reactions to IV iron products. The concurrence of events may be explained by one or more known mechanisms. Thus, a description of events rather than attribution of events to Kounis Syndrome may be justified in labeling of IV iron products.

"Kounis Syndrome" does not currently appear on any approved drug labeling despite proposals by applicants to label the eponym. Previous DPV reviews of Kounis Syndrome have recommended an objective description of the event be placed in labeling rather than the eponym (Cotter and Woronow 2020b; Gish and Woronow 2020). DPV and subsequent Office of New Drugs (OND) objections to using the Kounis Syndrome eponym in labeling included: concern that the eponym may not be widely embraced or understood among U.S. healthcare providers; the term is not included in the 2020-ICD10-CM index; and debate in the medical literature about Kounis Syndrome (Cotter and Woronow 2020b; Gish and Woronow 2020; Debellas 2020; Davidson 2020; Voqui 2021). In fact, some authors are not convinced that the proposed Kounis Syndrome pathophysiology represents a distinct clinical entity; others dispute Dr. Kounis' conclusions and found his claims "astonishing" (Pinto et al. 2019; Witteles et al. 2016). While completing our review, we noted seeming omission of patients with symptomatic coronary artery disease (and not stents) among the described Kounis Syndrome variants, yet these patients would also presumably be vulnerable to Kounis Syndrome.

If DNH decides to include Kounis Syndrome in IV iron labeling, we prefer the addition be limited to an objective description of the event rather than a named syndrome that is not universally accepted in medicine. FDA labeling guidance discourages the use of terms that lack a commonly understood meaning.[o] Regarding Sanofi's proposed Ferrlecit labeling revisions, we disagree with placement of Kounis Syndrome in WARNINGS and PRECAUTIONS. The level of evidence does not support placement in WARNINGS and PRECAUTIONS at this time based on Guidance and 21 CFR 201.57.[p] Second, we disagree with Sanofi's proposal to place Kounis Syndrome in AR CTE because the data came from postmarketing reports, not clinical trial experience. However, we do not object to placement of an objective description of Kounis Syndrome in AR PME because there is limited basis (biological plausibility and temporal relationship) to believe there is a possible causal relationship between the events and IV iron products. [o]

5 CONCLUSION

Despite wide use and many years of marketing we identified only four cases of IV iron product use that may be associated with Kounis Syndrome and they met the lower of two tiers (Tier B) in

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[o] Guidance for industry, *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[p] Guidance for industry, *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format*. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

DPV's case definition. We do not feel that the level of evidence supports the placement of "Kounis Syndrome" in IV iron product labeling, but we do not object to the inclusion of an objective description of events in the ADVERSE REACTIONS, Postmarketing Experience section. DNH should consider that adding "Kounis Syndrome" to labeling would be the first inclusion of this term in any FDA approved labeling.

6 RECOMMENDATIONS

We prefer that any addition to labeling be limited to an objective description of the event, rather than a named syndrome that is not universally accepted in medicine and may not be commonly understood. An example of such text could be, "acute myocardial ischemia with or without myocardial infarction, or in-stent thrombosis, may occur in the context of a hypersensitivity reaction."

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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.2 APPENDIX B. FAERS LINE LISTING OF KOUNIS SYNDROME WITH IV IRON PRODUCTS CASE SERIES (N=4)

[Duplicate reports are in brackets.]

Ref #	FAERS Case #	Initial FDA Received Date	Version #	Manufacturer Control #	Report Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
1	6920633 [5793538] [7242745]	02/12/2009	1	20090038 [2005-01398] [20090583]	Expedited	37	Female	USA	HO
2	9670358	11/04/2013	2	AMAG201300187	Expedited	70	Male	Canada	DE, HO, LT, OT
3	10238870	06/12/2014	1	20140321	Expedited	57	Male	China	HO, LT
4	11228784	06/29/2015	1	Not applicable	Direct	63	Female	USA	LT, OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A case can have more than one serious outcome.
Abbreviations: DE=death, HO=hospitalization, LT= life-threatening, OT=other medically significant

8.3 APPENDIX C. FAERS CLINICAL CASE SUMMARIES OF KOUNIS SYNDROME WITH IV IRON CASE PRODUCTS CASE SERIES (N=4)

Ref # **Date Received** **Country** **FAERS Case-Version #** **Citation (if applicable)**	**Age (years)/sex** **IV Iron/Dose** **Indication**	**Time to Onset** **Symptoms**	**Immunomodul-ators given?** **Epinephrine, vasopressor given acutely?** **Anti-vasospastic agent given? (e.g., calcium channel blocker, nitroglycerin)**	**Inflammatory mediators and other tests consistent with hypersensitivity**	**Coronary angiogram** **Cardiac biomarkers**	**Regulatory Outcome*** **Clinical Outcome**	**Kounis Variant Type, Evidence Tier** **WHO Causality** **Comments**
1 02/12/2009 USA 6920633-1 Ahluwalia et al. 2004	37/Female Iron dextran (Dexferrum)/dose not reported Iron deficiency anemia secondary to blood loss	"Immediately after the infusion" (first dose) Severe chest pain, shortness of breath, hypotension	Yes: unspecified steroids, unspecified antihistamines None reported None reported	None reported	"No evidence of coronary artery disease; mild impairment of left ventricular systolic function with hypokinesis of the apex and distal anterior and anterolateral wall with ejection fraction around 45%" "Troponin was elevated at 2.7 (RR 0-0.25)" (units not reported) "EKG did not show evidence of ST changes suggestive of ischemia"	HO Recovered ("discharged home second day after catheterization")	Type I, Tier B Possible The authors stated: "MI was most likely induced by coronary vasospasm and hypotension secondary to anaphylactic reaction." Other possible explanations for NSTEMI include acute hypotension and severe anemia although authors did not provide hemoglobin levels nor history of events leading to hemorrhage and iron infusion (Thygesen et al. 2018).
2 11/04/2013 Canada 9670358-2	70/Male Ferumoxytol (Feraheme)/ 510mg	Hypersensitivity reaction – during infusion (second dose). Acute coronary event –	Yes: diphenhydramine, ranitidine, methylprednisolone	None reported	Distal right coronary artery thrombosis No cardiac biomarkers reported.	DE, HO, LT, OT Death: "He arrested and	Type II, Tier B Possible Significant history of

Ref # Date Received Country FAERS Case-Version # Citation (if applicable)	Age (years)/sex IV Iron/Dose Indication	Time to Onset Symptoms	Immunomodul-ators given? Epinephrine, vasopressor given acutely? Anti-vasospastic agent given? (e.g., calcium channel blocker, nitroglycerin)	Inflammatory mediators and other tests consistent with hypersensitivity	Coronary angiogram Cardiac biomarkers	Regulatory Outcome* Clinical Outcome	Kounis Variant Type, Evidence Tier WHO Causality Comments
	Iron deficiency anemia	unspecified hours later Flushing, vision loss, difficulty breathing, itchiness of head and whole body, diaphoretic, non-responsive, hypotensive (60/40mmHg). Hours later, acute chest pain with ECG changes and acute pulmonary edema	None reported None reported		Unspecified "ECG changes"	ultimately expired" the day after Feraheme administration.	coronary artery disease (MI 15 years prior, CABG x4 21 years prior), weak support for coronary vasospasm (acute chest pain with ECG changes) before coronary thrombosis imaged
3 06/12/2014 China 10238870-1 Hou et al. 2014	57/Male Iron sucrose (Venofer)/ dose not reported Iron deficiency anemia	During infusion (second dose) Dyspnea, malaise, sweating, continuous coughing, pink frothy sputum, hypotension (to 60/40mmHg), HR increased (to 140bpm)	None reported Yes: dopamine, norepinephrine Yes: unspecified; "treatment with a vasoactive agent"	None reported. Day 8 IgE was within normal limits.	"70-80% diffuse lesion in the mid-distal end of the left circumflex artery (LCx) with TIMI grade 3 flow" Repeat coronary angiography admission day 24: no lesions troponin I > 50 mcg/L (RR 0-0.15 mcg/L)	HO, LT Recovered	Type I, Tier B Probable See Reviewer Comments in Section 3.1

Ref # Date Received Country FAERS Case-Version # Citation (if applicable)	Age (years)/sex IV Iron/Dose Indication	Time to Onset Symptoms	Immunomodul-ators given? Epinephrine, vasopressor given acutely? Anti-vasospastic agent given? (e.g., calcium channel blocker, nitroglycerin)	Inflammatory mediators and other tests consistent with hypersensitivity	Coronary angiogram Cardiac biomarkers	Regulatory Outcome* Clinical Outcome	Kounis Variant Type, Evidence Tier WHO Causality Comments
					ST-segment elevation in leads I and aVL "indicated acute lateral wall STEMI + slightly impaired left lateral ventricular contraction and no mechanical complications"		
4 06/29/2015 USA 11228784-1	63/Female SFGC (Ferrlecit)/ 250mg Iron deficiency anemia secondary to blood loss	During infusion (1.5 hours from start of infusion) (first dose) Hives, itching, hypotensive, diaphoretic, cool extremities	Yes: diphenhydramine, famotidine None reported None reported	None reported.	"Left heart catheterization revealed in-stent thrombosis" No cardiac biomarkers reported. "EKG revealed ST elevations"	LT, OT	Type III/Tier B Possible See Reviewer Comments in Section 3.1

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A case can have more than one serious outcome.
Abbreviations: DE=death, ECG or EKG: electrocardiogram, HO=hospitalization, LT= life-threatening, NSTEMI=Non-ST-elevation myocardial infarction, OT=other medically significant, SFGC=sodium ferric gluconate complex

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DANIELLE M MOLNAR
02/11/2022 10:43:14 AM

CHRISTINA E HANTSCH BARDSLEY
02/11/2022 12:26:04 PM

MALLIKA L MUNDKUR
02/11/2022 02:20:03 PM

STEVEN C JONES
02/11/2022 02:22:35 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 212340

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

FDA U.S. FOOD & DRUG ADMINISTRATION

ANDA 212340

DISCIPLINE REVIEW LETTER
LABELING

Sandoz Inc
100 College Road West
Princeton, NJ 08540
Attention: Gregory Seitz
Head, U.S. Regulatory Affairs Generics

Dear Gregory Seitz:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on August 18, 2023, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Iron Sucrose Injection USP, 50 mg Elemental Iron/2.5 mL (20 mg/mL), 100 mg Elemental Iron/5 mL (20 mg/mL), 200 mg Elemental Iron/10 mL (20 mg/mL) (Single-Dose Vials).

Reference is also made to any amendments submitted prior to the issuance of this letter.

The following possible deficiencies have been identified by Labeling:

LABELING

(b)(4)

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated

and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the Electronic Orange Book are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

If you would like to respond to these possible deficiencies before the end of this review cycle, we request a complete written response to this discipline review letter (DRL) no later than June 9, 2025. If you submit a written response during this review cycle, depending on the timing and/or the information contained in your response, we may not be able to consider your response before taking action on your application. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
LABELING
MINOR

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2022 (GDUFA III)[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified or additional deficiencies may be identified as we complete our review of your entire application.

Deficiencies addressed by applicants in a response to a DRL may appear in a Complete Response Letter (CRL) if FDA's review of the response has been deferred or if FDA has outstanding concerns after review of the response. The CRL will include all deficiencies that must be satisfactorily addressed before the ANDA can be approved.

If the applicant receives a CRL, but has already responded to some (or all) identified deficiencies in a DRL response, the applicant does not need to re-submit previously submitted information in a CRL amendment. However, the applicant should still submit a CRL amendment and should clearly identify the previously provided DRL response that renders its CRL amendment complete.

Additionally, please take note of the following if you choose to respond to these possible deficiencies before the end of this review cycle:

1. If your submission is a response to a Major DRL received by the due date (or any agreed-upon extension), FDA may classify the response as Major and assign an appropriate goal date for that amendment.

2. If you do not respond by the requested due date, FDA may defer review of your response.

3. FDA will strive to review your response during the review cycle in which it is received if such review can be completed during such review cycle. However, if the Agency determines that it cannot review the response before a goal date or if a complete response letter is otherwise ready to be issued, the review of your response may be deferred. When FDA defers review of your response, it will be reviewed during the next review cycle for the application.

4. If you are responding to a late cycle DRL[2], the goal date may be extended based upon the major or minor deficiencies included upon receipt of the response.

5. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as a major or minor amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

As described in FDA's draft guidance for industry *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions*, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, please contact Juliette Larmie-Gyamfi, Labeling Project Manager, at Juliette.Larmie-Gyamfi@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Juliette Larmie-Gyamfi
Labeling Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

[1] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023-2027 (available at:https://www.fda.gov/media/153631/download).
[2] Late cycle defined as IRs or DRLs issued after the mid-cycle of an original ANDA or IRs or DRLs issued less than 90 days from the goal date of an ANDA amendment

ANDA 212340

DISCIPLINE REVIEW LETTER
LABELING

Sandoz Inc
100 College Road West
Princeton, NJ 08540
Attention: Gregory Seitz
Head, U.S. Regulatory Affairs Generics

Dear Gregory Seitz:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on August 18, 2023, April 4, 2024, and August 5, 2024submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Iron Sucrose Injection USP, 50 mg Elemental Iron/2.5 mL (20 mg/mL), 100 mg Elemental Iron/5 mL (20 mg/mL), 200 mg Elemental Iron/10 mL (20 mg/mL) (Single-Dose Vials).

Reference is also made to any amendments submitted prior to the issuance of this letter.

1. GENERAL COMMENTS

On April 15, 2016, Foley Hoag LLP submitted a Citizen Petition (Docket No. FDA-2016-P-1163) requesting, among other things, that FDA recognize that Velphoro (new drug application (NDA) 205109) is eligible for 5-year new chemical entity (NCE) exclusivity under 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (Velphoro Citizen Petition). On May 26, 2021, FDA published a response to the Velphoro Citizen Petition in which we denied the request, among other things, and determined that Velphoro's active moiety and active ingredient are ferric oxyhydroxide.

Following publication of the Velphoro Citizen Petition response, the Agency accordingly issued a revised draft product-specific guidance (PSG), updated the Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book) and Drugs@FDA. Please be advised that the agency intends to consider additional regulatory actions and/or policy changes to address certain issues implicated by this petition response.

Additionally, on August 3, 2021, Vifor (International) Inc., Switzerland (Vifor) submitted a Citizen Petition and Petition for Stay (Docket No.

FDA-2021-P-0893) (Vifor Petition) requesting the Agency reverse certain actions announced in its Velphoro Citizen Petition response. The issues raised by the Vifor petition are under review by the Agency, and FDA has not made a final decision on these issues. On July 1, 2024, the Agency published a memorandum stating that the Center for Drug Evaluation and Research (CDER) "is reevaluating its determination that the active ingredient of the iron products subject to the May 26, 2021, Citizen Petition response is ferric oxyhydroxide." The memorandum also stated that during the reevaluation period, "CDER is accepting the active ingredient names as approved prior to the May 26, 2021, Citizen Petition response for all iron products subject to the May 26, 2021, Citizen Petition response..." (See Docket Nos FDA-2016-P-1163 and FDA-2021-P-0893, available at regulations.gov.).

Also note that Sonnenschein, Nath & Rosenthal LLP submitted a Citizen Petition (Docket No. FDA-2005-P-0319) (Venofer Citizen Petition) requesting, among other things, that the FDA adopt and apply certain requirements to ensure "the even-handed application of the requirements of Section 505 of the [FD&C Act] and the safety and efficacy of any generic version or pharmaceutical equivalent" of Venofer (Venofer Citizen Petition, at 2). The issues raised by that petition are under review by the Agency, and the FDA has not made a final decision on these issues.

2. CONTAINER LABEL
    a. Decrease the prominence of the net quantity statement (i.e., 2.5 mL Single-Dose Vial, 5 mL Single-Dose Vial, 10 mL Single-Dose Vial) on all container labels so that it does not compete with the most critical information (e.g., established name, strength, route of administration, etc.), on the principal display panel (PDP). Refer to the Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors | FDA.
    b. Revise the route of administration to title case (i.e., "For Intravenous Use Only") to be same as the RLD.

3. CARTON LABELING
    a. Side Panel: Add the word "Sterile" following the storage temperatures on all carton labeling to be same as the RLD.
    b. Side Panel: Revise (b)(4) to "Sodium hydroxide may be added to adjust pH to 10.5 to 11.1." on all carton labeling to be same as the RLD.
    c. Refer to the comment under 1b.

4. PRESCRIBING INFORMATION

a. HOW SUPPLIED/STORAGE AND HANDLING: Add the "USP" descriptor to the HOW SUPPLIED/STORAGE AND HANDLING section.
b. HOW SUPPLIED/ STORAGE AND HANDLING: Add your product description (e.g., shape, color, scoring, coating, and imprint code) to be in accordance with the information in your submission, as required per 21 CFR 201.57(c)(17).
c. HOW SUPPLIED/STORAGE AND HANDLING: Add "Discard unused portion" to this section as the proposed product is for a single-dose container. Refer to the Guidance for Industry - Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Container for Human Use.

LABELING

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the Electronic Orange Book are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

If you would like to respond to these possible deficiencies before the end of this review cycle, we request a complete written response to this discipline review letter (DRL) no later than June 2, 2025. If you submit a written response during this review cycle, depending on the timing and/or the information contained in your response, we may not be able to consider your response before taking action on your application. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
LABELING
MINOR

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2022 (GDUFA III)[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified or additional deficiencies may be identified as we complete our review of your entire application.

Deficiencies addressed by applicants in a response to a DRL may appear in a Complete Response Letter (CRL) if FDA's review of the response has been deferred or if FDA has outstanding concerns after review of the response. The CRL will include all deficiencies that must be satisfactorily addressed before the ANDA can be approved.

If the applicant receives a CRL, but has already responded to some (or all) identified deficiencies in a DRL response, the applicant does not need to re-submit previously submitted information in a CRL amendment. However, the applicant should still submit a CRL amendment and should clearly identify the previously provided DRL response that renders its CRL amendment complete.

Additionally, please take note of the following if you choose to respond to these possible deficiencies before the end of this review cycle:

1. If your submission is a response to a Major DRL received by the due date (or any agreed-upon extension), FDA may classify the response as Major and assign an appropriate goal date for that amendment.

2. If you do not respond by the requested due date, FDA may defer review of your response.

3. FDA will strive to review your response during the review cycle in which it is received if such review can be completed during such review cycle. However, if the Agency determines that it cannot review the response before a goal date or if a complete response letter is otherwise ready to be issued, the review of your response may be deferred. When FDA defers review of your response, it will be reviewed during the next review cycle for the application.

4. If you are responding to a late cycle DRL[2], the goal date may be extended based upon the major or minor deficiencies included upon receipt of the response.

5. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by

FDA, FDA may classify the response as a major or minor amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

As described in FDA's draft guidance for industry *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions*, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, please contact Juliette Larmie-Gyamfi, Labeling Project Manager, at Juliette.Larmie-Gyamfi@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Juliette Larmie-Gyamfi
Labeling Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

[1] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023-2027 (available at:https://www.fda.gov/media/153631/download).
[2] Late cycle defined as IRs or DRLs issued after the mid-cycle of an original ANDA or IRs or DRLs issued less than 90 days from the goal date of an ANDA amendment

ANDA 212340

AMENDMENT ACKNOWLEDGEMENT
Standard
Major

Sandoz Inc.
100 College Road West
Princeton, NJ 08540
Attention: Gregory Seitz
Executive Director, Regulatory Affairs

Dear Gregory Seitz:

This is in reference to your amendment received on August 18, 2023, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Iron Sucrose Injection USP, 50 mg Elemental Iron/2.5 mL (20 mg/mL), 100 mg Elemental Iron/5 mL (20 mg/mL) and 200 mg Elemental Iron/10 mL (20 mg/mL) Single-Dose Vials.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2022 (GDUFA III). FDA has made an initial determination that this is a standard major amendment. If FDA determines that an inspection is not required to validate the information contained in this standard major amendment, the GDUFA goal date for review of this standard major amendment is April 18, 2024. If this standard major amendment requires an inspection, the goal date for review of this standard major amendment is June 18, 2024. Two possible goal dates are provided because FDA is unable to determine if an amendment requires an inspection at the time of submission. FDA will make this determination during the assessment of the amendment. For more information, see FDA's Guidance for Industry, *ANDA Submissions - Amendments to Abbreviated New Drug Applications Under GDUFA.*

GDUFA provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the reference listed drug (RLD) that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

As described in FDA's Draft Guidance for Industry, *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions*, FDA recommends that you

include the appropriate attachment(s) along with the cover letter for your submission to help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, please contact Parth Soni, Regulatory Project Manager, at (301) 796-7673.

Sincerely,

{See appended electronic signature page}

Parth Soni, PharmD, MBA, PMP
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

ANDA 212340

INFORMATION REQUEST
QUALITY

Sandoz Inc.
100 College Road West
Princeton, NJ 08540
Attention: Gregory Seitz
Executive Director, Regulatory Affairs

Dear Gregory Seitz:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on August 28, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Iron Sucrose Injection USP, 50 mg Elemental Iron/2.5 mL (20 mg/mL), 100 mg Elemental Iron/5 mL (20 mg/mL) and 200 mg Elemental Iron/10 mL (20 mg/mL).

We also refer to your December 28, 2020 submission, containing complete response.

We are reviewing the Quality section of your submission and have the following comments and information requests:

A. Manufacturing

Process

1. (b)(4)

We request a prompt written response, no later than July 7, 2022 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY/MANUFACTURING PROCESS

If you have any questions, please contact Erin Andrews, Regulatory Business Process Manager, at erin.andrews@fda.hhs.gov or (240) 402 - 8578.

Sincerely,

{See appended electronic signature page}

Erin Andrews, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Erin Andrews

Digitally signed by Erin Andrews
Date: 6/16/2022 10:54:41AM
GUID: 52e7d3790000f03cf7ec38aacca759ed

ANDA 212340

INFORMATION REQUEST
QUALITY

Sandoz Inc.
100 College Road West
Princeton, NJ 08540
Attention: Gregory Seitz
Executive Director, Regulatory Affairs

Dear Gregory Seitz:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on August 28, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Iron Sucrose Injection USP, 50 mg Elemental Iron/2.5 mL (20 mg/mL), 100 mg Elemental Iron/5 mL (20 mg/mL) and 200 mg Elemental Iron/10 mL (20 mg/mL).

We also refer to your December 28, 2020 submission, containing complete response.

We are reviewing the Quality section of your submission and have the following comments and information requests:

A. Drug Substance

1.

2. (b)(4)

b. (b)(4)

Comment:

Please note that Foley Hoag LLP submitted a Citizen Petition [Docket ID: FDA- 2016-P-1163] requesting, among other things, that FDA recognize that Velphoro (new drug application (NDA) 205109) is eligible for 5-year new chemical entity (NCE) exclusivity under 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the Federal, Food, Drug, and Cosmetic Act (FD&C Act) (Velphoro Citizen Petition). On May 26, 2021, FDA published a response to the Velphoro Citizen Petition in which we denied the request, among other things, and determined that Velphoro's active moiety and active ingredient is ferric oxyhydroxide. In the response, we state that "ferric oxhydroxide is responsible for the pharmacological activity of both Velphoro and Venofer, and is thus the active ingredient in both drug products under the regulatory definition of "active ingredient" and additionally, "[s]ucrose and starches are merely excipients providing stability and processes functions…" (Reference: FDA Letter Response to Citizen Petition (CP), Docket No. FDA-2016-P-1163, at 40 (May 26, 2021) (Velphoro Petition Response), available at: https://downloads.regulations.gov/FDA-2016-P-1163-0097/attachment_1.pdf.) Therefore, it is the Agency's conclusion that the active ingredient of Venofer is Ferric Oxyhydroxide and sucrose is an excipient. Accordingly, we recommend you review the Agency's response and make any appropriate revisions to your application.

Please be advised that the agency intends to consider additional regulatory actions and/or policy changes to address certain issues implicated by this petition response, which may result in additional requests in future response letters to this application.

B. Drug Product

1.

2. (b)(4)

3.

C. Manufacturing

Process

1. (b)(4)

2. (b)(4)

We request a prompt written response, no later than November 29, 2021 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY/DRUG SUBSTANCE/DRUG PRODUCT/MANUFACTURING PROCESS

If you have any questions, please contact Erin Andrews, Regulatory Business Process Manager, at erin.andrews@fda.hhs.gov or (240) 402 - 8578.

Sincerely,

{See appended electronic signature page}

Erin Andrews, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Erin Andrews

Digitally signed by Erin Andrews
Date: 10/26/2021 11:13:48AM
GUID: 52e7d3790000f03cf7ec38aacca759ed

FDA U.S. FOOD & DRUG ADMINISTRATION

ANDA 212340

AMENDMENT ACKNOWLEDGEMENT
Standard
Major

Sandoz Inc.
100 College Road West
Princeton, NJ 08540
Attention: Gregory Seitz
Executive Director, Regulatory Affairs

Dear Sir:

This is in reference to your amendment received on December 28, 2020, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Iron Sucrose Injection USP, 50 mg Elemental Iron/2.5 mL (20 mg/mL), 100 mg Elemental Iron/5 mL (20 mg/mL) and 200 mg Elemental Iron/10 mL (20 mg/mL) Single-Dose Vials.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). FDA has made an initial determination that this is a standard major amendment. If FDA determines that an inspection is not required to validate the information contained in this standard major amendment, the GDUFA goal date for review of this standard major amendment is August 27, 2021. If this standard major amendment requires an inspection, the goal date for review of this standard major amendment is October 27, 2021. Two possible goal dates are provided because FDA is unable to determine if an amendment requires an inspection at the time of submission. FDA will make this determination during the assessment of the amendment. For information, see FDA's guidance for industry, *ANDA Submissions - Amendments to Abbreviated New Drug Applications Under GDUFA.*

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

If you have any questions, please contact Parth Soni, Regulatory Project Manager, at (301) 796-7673.

Sincerely,

{See appended electronic signature page}

Parth Soni, PharmD, PMP
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

ANDA 212340

COMPLETE RESPONSE

Sandoz Inc.
100 College Road West
Princeton, NJ 08540
Attention: Gregory Seitz
Executive Director, Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on August 28, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Iron Sucrose Injection USP, 50 mg Elemental Iron/2.5 mL (20 mg/mL), 100 mg Elemental Iron/5 mL (20 mg/mL) and 200 mg Elemental Iron/10 mL (20 mg/mL) Single-Dose Vials.

Reference is also made to any amendments submitted prior to the issuance of this letter.

We also acknowledge receipt of your amendment received on April 16, 2020, which was deferred and not reviewed for this action. You may incorporate applicable sections of the deferred amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PHARMACEUTICAL QUALITY

Drug Substance

The Pharmaceutical Quality deficiencies have been classified as MAJOR due to the nature of the deficiencies identified in Drug Master File (DMF) [redacted] (see guidance for industry ANDA Submissions – Amendments to Abbreviated New Drug Applications Under GDUFA). The deficiencies were communicated to the DMF holder in a separate Complete Response Letter. Contact the referenced DMF holder for more information.

1. (b)(4)

2.

(b)(4)

3.

Drug Product

4.

(b)(4)

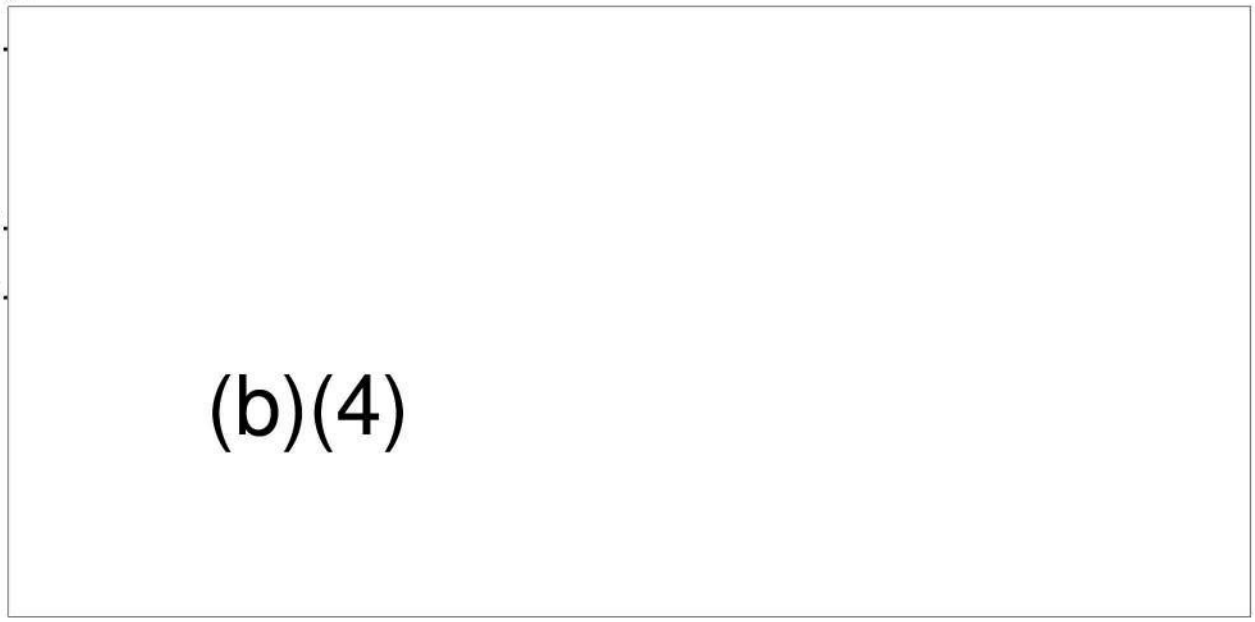
(b)(4)

(b)(4)

11.

12.

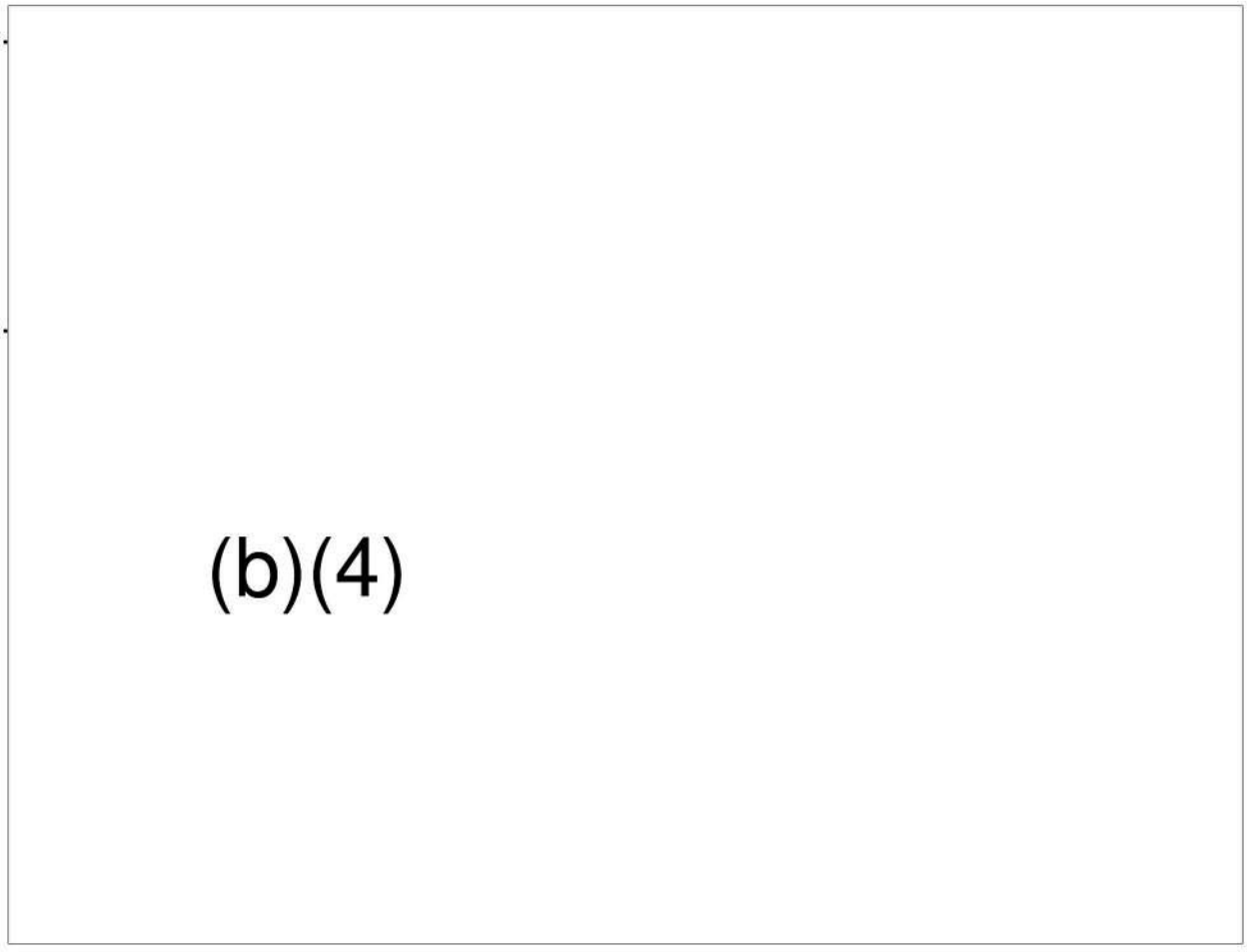
13.



Process

14.

15.



16. (b)(4)

Microbiology

The Pharmaceutical Quality deficiencies have been classified as MAJOR because media fill process simulation data supporting the use of the appropriate filling line/machine for your aseptically filled drug product was not provided, as noted in Appendix A, Section A(4)(d) of the *Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA* (July 2018). This information is required to support drug product sterility assurance. Upon receipt, in FDA's judgement, the review of this information will require substantial expenditure of FDA resources

17.

18.

19. (b)(4)

(b)(4)

(b)(4)

(b)(4)

BIOEQUIVALENCE

The Bioequivalence deficiencies have been classified as MAJOR because the deficiencies pertain to insufficient method validation data. As noted in Appendix A, Section B(1)(a) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). Upon receipt, in FDA's judgement, the review of this information will require substantial expenditure of FDA resources.

Pivotal Fasting Bioequivalence Study(#RFR-P5-709)

1. You rejected analytical batches for both total serum iron and transferrin-bound iron assays based on "The coefficient of determination was (b)(4)". However, this criterion was not documented in your standard operation procedure (SOP) No. (b)(4). Please provide evidence to support why you pre-set (b)(4) as R^2 cutoff.

Particle Size Distribution (PSD) Study

2. Please submit SOP for method validation of PSD study by dynamic light scattering. Please also provide study date for your PSD study.

3. You used five test product batches (two demo batches: #IRSUS/22, IRSUS/25; three exhibit batches: 801859, 801863, and 801869) in PSD study. Please clarify if there is any difference among all five test product batches,) in terms of manufacturing process, in-process controls and specifications.

4. You used test product (lot #IRSUS/25, 2017 demo batch) to conduct pre-study method validation for precision (Study report No. IRSUS_AMV_REP_DP_DLS_V01). Since the test product is not an approved drug product at the time of submission, it is not appropriate to be used in method validations. Please repeat pre-study method validation for precision, intermediate precision, repeatability and ruggedness using the reference product.

5. For PSD study by dynamic light scattering, you stated that you performed two measurements per preparation and reported the results as arithmetic average of two measurements for each preparation. Please provide in vitro testing data with every individual measurement in SAS transport file (.xpt) using the following format.

PRODUCT	LOT	VIAL/Measurement		D10	D50	D90	SPAN	Polydispersity Index
TEST	1234	1	Measurement 1					
			Measurement 2					
		1	Measurement 1					
			Measurement 2					
		1	Measurement 1					
			Measurement 2					
		2	Measurement 1					
			Measurement 2					
		2	Measurement 1					
			Measurement 2					
		2	Measurement 1					
			Measurement 2					
		n	Measurement 1					
			Measurement 2					
		n	Measurement 1					
			Measurement 2					
		n	Measurement 1					
			Measurement 2					

FDA publishes new and revised product-specific guidances describing the Agency's current recommendations on demonstrating bioequivalence and certain other approval requirements. To ensure you are aware of FDA's recommendations for the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence (21 CFR 320.24(a)), please continue to monitor for the availability of new and revised product-specific guidances in the *Federal Register* and on the FDA Web site at the following address: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

FACILITY INSPECTION / LABELING

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of the date the discipline review was completed. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally, the compliance status of each facility named in the application may be re-evaluated upon re-submission.

We remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure that your ANDA addresses all listed patents and exclusivities that claim the approved drug product. Please ensure that all exclusivities

and patents listed in the Electronic Orange Book are addressed and updated in your application. Also, ensure that your labeling aligns with your patent and exclusivity statements.

OTHER

The resubmission to this CR letter will be considered to represent a **MAJOR** AMENDMENT, given that the deficiencies have been classified as **MAJOR**.

Prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission. If your submission includes gratuitous information in addition to the category or categories below, clearly identify the type of information submitted immediately following the wording below:

RESUBMISSION
MAJOR
COMPLETE RESPONSE AMENDMENT
DRUG SUBSTANCE / DRUG PRODUCT / PROCESS / MICROBIOLOGY / BIOEQUIVALENCE

Upon review of your amendment, FDA may identify information in the amendment that may require a change in classification and an adjustment to the goal date.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response as a request to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter does not fulfill the requirements in 21 CFR 314.110(b)(1) and therefore will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that

it will be a violation of federal law to ship these products in interstate commerce or import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including by fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure you stay up to date with the Agency's current thinking on topics through guidances for industry, including product-specific guidances.

If you have any questions, call Parth Soni, PharmD, Regulatory Project Manager, Division of Project Management, at (301) 796-7673.

Sincerely yours,

{See appended electronic signature page}

Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

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[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

Denise
Toyer McKan

Digitally signed by Denise Toyer McKan
Date: 6/26/2020 07:44:49AM
GUID: 5277df670008860f7e1231f730a8684c

FDA U.S. FOOD & DRUG ADMINISTRATION

(b)(4)

The purpose of this letter is to inform you in writing of the outcome of a U.S. Food and Drug Administration (FDA) inspection conducted at (b)(4) by Dr. Sripal R. Mada. No objectional conditions or practices were found during the inspection. No response to this letter is necessary.

The FDA conducted this inspection under its Bioresearch Monitoring Program, which includes inspections designed to ensure that data and information submitted to FDA are scientifically valid and reliable. Another objective of the program is to ensure that the rights, welfare, and safety of research subjects are protected during the study of an investigational product.

This inspection was conducted by FDA to determine whether your activities and procedures complied with Title 21, Code of Federal Regulations (CFR) Part 320 - Bioavailability and Bioequivalence (BE).

We appreciate the cooperation you showed to FDA's Dr. Mada during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please send all correspondence to:

CDER-OSIS-BEQ@fda.hhs.gov

OR

Office of Study Integrity and Surveillance
Office of Translational Sciences
Center for Drug Evaluation and Research
Food and Drug Administration
Building 22, Room 1471
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely,

Seongeun Cho -S

Digitally signed by Seongeun Cho -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Seongeun Cho -S, 0.9.2342.19200300.100.1.1=2000336978
Date: 2020.05.28 13:50:17 -04'00'

Seongeun (Julia) Cho
Director
Division of Generic Drug Study Integrity
Office of Study Integrity and Surveillance
Office of Translational Sciences
Center for Drug Evaluation and Research
United States Food and Drug Administration

ANDA 212340

INFORMATION REQUEST

Sandoz Inc
100 College Road West
Princeton, NJ 08540
Attention: Gregory Seitz
Executive Director, Regulatory Affairs

Dear Gregory Seitz:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on August 28, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Iron Sucrose Injection, USP Eq. 20 mg base/mL.

We are reviewing the Quality section of your submission and have the following comments and information requests:

A. Drug Product

1. (b)(4)

We request a prompt written response, no later than **April 24, 2020** in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date

assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY

If you have any questions, please contact Temitope Oriola, PharmD, Regulatory Business Process Manager, at Temitope.Oriola@fda.hhs.gov or (240) 402 - 4646.

Sincerely,

{See appended electronic signature page}

Temitope Oriola, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Temitope Oriola

Digitally signed by Temitope Oriola
Date: 3/25/2020 10:52:54AM
GUID: 56f4536500ea9700421d7152e24f140d

FDA U.S. FOOD & DRUG ADMINISTRATION

ANDA 212340

INFORMATION REQUEST

Sandoz Inc.
100 College Road West
Princeton, NJ 08540
Attention: Gregory Seitz
Executive Director, Regulatory Affairs

Dear Gregory Seitz:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 28, 2020, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Iron Sucrose Injection USP 50 mg/2.5 mL, 100 mg/5 mL, 200 mg/10 mL.[1]

We are reviewing the Quality section of your submission and have the following comments and information requests:

A. Drug Substance:

1. (b)(4)

B. Drug Product

1. (b)(4)

[1] The active ingredient is referred to as "iron sucrose" as submitted in your Amendment submitted on 12/7/2021. However, as noted previously in our correspondence to you dated October 26, 2021 and as you acknowledged, it is the Agency's scientific conclusion that the active ingredient of Venofer is ferric oxyhydroxide and sucrose is an excipient. References to "iron sucrose" throughout these preliminary responses reflect references made in your submission, but do not reflect current Agency thinking." See Docket FDA- 2016-P-1163 and Docket FDA-2021-P-0893.

2. (b)(4)

3.

C. **Manufacturing**

1. **Process**

a. (b)(4)

We request a prompt written response, no later than April 22, 2022 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

U.S. Food & Drug Administration
Silver Spring, MD 20993
www.fda.gov

INFORMATION REQUEST
QUALITY

If you have any questions, please contact Andrea Storey, Regulatory Business Process Manager, at andrea.storey@fda.hhs.gov or (301) 348 - 1977.

Sincerely,

{See appended electronic signature page}

Andrea Storey
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Andrea Storey

Digitally signed by Andrea Storey
Date: 3/23/2022 08:53:25AM
GUID: 58ece2cb0014d753eda8f687212809d7

ANDA 212340

DISCIPLINE REVIEW LETTER
QUALITY

Sandoz Inc
100 College Road West
Princeton, NJ 08540
Attention: Gregory Seitz
Executive Director, Regulatory Affairs

Dear Gregory Seitz:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on August 28, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Iron Sucrose Injection, USP Eq. 20 mg base/mL.

The following possible deficiencies have been identified by the Office of Pharmaceutical Quality:

A. Drug Substance

1.

2. (b)(4)

3.

B. Drug Product

1. (b)(4)

(b)(4)

(b)(4)

C. Manufacturing

a. Process

1.

2.

(b)(4)

3.

D. Microbiology

1.

2.

3.

4.

(b)(4)

5.

6.

(b)(4)

(b)(4)

(b)(4)

If you would like to respond to these possible deficiencies before the end of this review cycle, we request a complete written response to this discipline review letter (DRL) no later than **March 26, 2020**. If you submit a written response during this review cycle, depending on the timing and/or the information contained in your response, we may not be able to consider your response before taking action on your application. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
QUALITY

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified or additional deficiencies may be identified as we complete our review of your entire application.

Deficiencies addressed by applicants in a response to a DRL may appear in a Complete Response Letter (CRL) if FDA's review of the response has been deferred or if FDA has outstanding concerns after review of the response. The CRL will include all deficiencies that must be satisfactorily addressed before the ANDA can be approved.

If the applicant receives a CRL, but has already responded to some (or all) identified deficiencies in a DRL response, the applicant does not need to re-submit previously submitted information in a CRL amendment. However, the applicant should still submit a CRL amendment and should clearly identify the previously provided DRL response that renders its CRL amendment complete.

Additionally, please take note of the following if you choose to respond to these possible deficiencies before the end of this review cycle:

1. FDA will strive to review your response during the review cycle in which it is received if such review can be completed during such review cycle. However, if the Agency determines that it cannot review the response before a goal date or if a complete response letter is otherwise ready to be issued, the review of your response may be deferred. When FDA defers review of your response, it will be reviewed during the next review cycle for the application.

2. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

If you have any questions, please contact Temitope Oriola, PharmD, Regulatory Business Process Manager, at Temitope.Oriola@fda.hhs.gov or (240) 402 - 4646.

Sincerely,

{See appended electronic signature page}

Temitope Oriola, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

[1] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at:https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

Temitope Oriola

Digitally signed by Temitope Oriola
Date: 2/26/2020 10:44:12PM
GUID: 56f4536500ea9700421d7152e24f140d

ANDA 212340

DISCIPLINE REVIEW LETTER
BIOEQUIVALENCE

Sandoz Inc.
100 College Road West
Princeton, NJ 08540
Attention: Gregory Seitz, Executive Director, Regulatory Affairs

Dear Gregory Seitz:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on August 28, 2019), submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Iron Sucrose Injection USP, 50 mg/2.5 mL (20 mg/mL),100 mg/5 mL (20 mg/mL) and 200 mg/10 mL (20 mg/mL) single-use vials.

The following possible deficiencies have been identified by BIOEQUIVALENCE:

Deficiency Related to the Pivotal Fasting Bioequivalence Study(#RFR-P5-709):

1. You rejected analytical batches for both total serum iron and transferrin-bound iron assays based on "The coefficient of determination was (b)(4)". However, this criterion was not documented in your standard operation procedure (SOP) No. (b)(4) (b)(4) Please provide evidence to support why you pre-set (b)(4) as R2 cutoff.

Deficiencies Related to Particle Size Distribution (PSD) Study:

1. Please submit SOP for method validation of PSD study by dynamic light scattering. Please also provide study date for your PSD study.

2. You used five test product batches (two demo batches: #IRSUS/22, IRSUS/25; three exhibit batches: 801859, 801863, and 801869) in PSD study. Please clarify if there is any difference among all five test product batches,) in terms of manufacturing process, in-process controls and specifications.

3. You used test product (lot #IRSUS/25, 2017 demo batch) to conduct pre-study method validation for precision (Study report No. IRSUS_AMV_REP_DP_DLS_V01). Since the test product is not an approved drug product at the time of submission, it is not appropriate to be used in method validations. Please repeat pre-study method validation for precision, intermediate precision, repeatability and ruggedness using the reference product.

4. For PSD study by dynamic light scattering, you stated that you performed two measurements per preparation and reported the results as arithmetic average of two measurements for each preparation. Please provide in vitro testing data with every individual measurement in SAS transport file (.xpt) using the following format.

PRODUCT	LOT	VIAL/Measurement		D10	D50	D90	SPAN	Polydispersity Index
TEST	1234	1	Measurement 1					
			Measurement 2					
		1	Measurement 1					
			Measurement 2					
		1	Measurement 1					
			Measurement 2					
		2	Measurement 1					
			Measurement 2					
		2	Measurement 1					
			Measurement 2					
		2	Measurement 1					
			Measurement 2					
		n	Measurement 1					
			Measurement 2					
		n	Measurement 1					
			Measurement 2					
		n	Measurement 1					
			Measurement 2					

If you submit a written response during this review cycle, depending on the timing and/or the information contained in your response, we may not be able to consider your response before taking action on your application. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
BIOEQUIVALENCE

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be

[1] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

modified or additional deficiencies may be identified as we complete our review of your entire application.

Deficiencies addressed by applicants in a response to a DRL may appear in a Complete Response Letter (CRL) if FDA's review of the response has been deferred or if FDA has outstanding concerns after review of the response. The CRL will include all deficiencies that must be satisfactorily addressed before the ANDA can be approved.

If the applicant receives a CRL, but has already responded to some (or all) identified deficiencies in a DRL response, the applicant does not need to re-submit previously submitted information in a CRL amendment. However, the applicant should still submit a CRL amendment and should clearly identify the previously provided DRL response that renders its CRL amendment complete.

Additionally, please take note of the following if you choose to respond to these possible deficiencies before the end of this review cycle:

1. FDA will strive to review your response during the review cycle in which it is received if such review can be completed during such review cycle. However, if the Agency determines that it cannot review the response before a goal date or if a complete response letter is otherwise ready to be issued, the review of your response may be deferred. When FDA defers review of your response, it will be reviewed during the next review cycle for the application.

2. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

If you have any questions, please contact Chyong-Yi Wu, Bioequivalence Project Manager, at Chyong-Yi.Wu@fda.hhs.gov or 301-796-4071.

Sincerely,

{See appended electronic signature page}

Chyong-Yi Wu, Ph.D.
Project Manager
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

James Buening

Digitally signed by James Buening
Date: 2/14/2020 04:59:12PM
GUID: 5d48976f001b770b910e6f447f20b77f

(b)(4)

(b)(4)

The purpose of this letter is to inform you in writing of the outcome of a U.S. Food and Drug Administration (FDA) inspection conducted at (b)(4) (b)(4) by Drs. Sripal Reddy Mada and Melkamu Getie Kebtie. No objectional conditions or practices were found during the inspection. No response to this letter is necessary.

The FDA conducted this inspection under its Bioresearch Monitoring Program, which includes inspections designed to ensure that data and information submitted to FDA are scientifically valid and reliable. Another objective of the program is to ensure that the rights, welfare, and safety of research subjects are protected during the study of an investigational product.

This inspection was conducted by investigators Drs. Mada and Getie-Kebtie to determine whether your activities and procedures complied with Title 21, Code of Federal Regulations (CFR) Part 320 - Bioavailability and Bioequivalence (BE) .

We appreciate the cooperation you showed to FDA investigators Drs. Mada and Getie-Kebtie during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please send all correspondence to:

CDER-OSIS-BEQ@fda.hhs.gov

OR

Office of Study Integrity and Surveillance
Office of Translational Sciences
Center for Drug Evaluation and Research
Food and Drug Administration
Building 22, Room 1471
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely,

John A. Kadavil -S

Digitally signed by John A. Kadavil -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300217653, cn=John A. Kadavil -S
Date: 2019.11.22 14:25:06 -05'00'

John Kadavil
Deputy Director
Division of Generic Drug Study Integrity
Office of Study Integrity and Surveillance
Office of Translational Sciences
Center for Drug Evaluation and Research
United States Food and Drug Administration

FDA U.S. FOOD & DRUG ADMINISTRATION

ANDA 212340

ACKNOWLEDGEMENT
ANDA RECEIPT

Sandoz Inc.
100 College Road West
Princeton, NJ 08540
Attention: Gregory Seitz

Dear Gregory Seitz:

This is in reference to your abbreviated new drug application (ANDA) submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The Food and Drug Administration (FDA or the Agency) has made a threshold determination that this ANDA is substantially complete. This ANDA is received for review.

NAME OF DRUG: Iron Sucrose Injection USP, 50 mg/2.5 mL (20 mg/mL),100 mg/5 mL (20 mg/mL) and 200 mg/10 mL (20 mg/mL) single-use vials

DATE OF APPLICATION: August 28, 2019

DATE (RECEIVED) ACCEPTABLE FOR REVIEW: August 28, 2019

This original ANDA is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). The GDUFA goal date for review of this standard original ANDA is June 27, 2020.

A drug with a name recognized in the USP National Formulary (USP–NF) generally must comply with applicable compendial standards or the drug will be deemed adulterated, misbranded, or both. (See section 501(b) and 502(e)(3)(b) and (g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); also 21 CFR 299.5(a) and (b)). Such drugs must also comply with compendial standards for strength, quality, and purity, unless labeled to show all respects in which the drug differs or they will be deemed adulterated. (See section 501(b) of the FD&C Act and 21 CFR 299.5(c)). If the proposed specifications for your product do not conform with an applicable official USP monograph, you are advised to contact USP upon receipt of this Acknowledgement Letter to initiate a monograph revision through the USP Pending Monograph Process (PMP). Please note that initiation of the PMP does not mean that the proposed specifications will necessarily be approved by FDA; revisions to the USP monograph will be contingent upon FDA approval of the proposed specifications in this application.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted

in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

Please identify any related communications with the ANDA number referenced above. If you have any questions, contact Wilbert Ferguson III, Regulatory Project Manager, at wilbert.ferguson@fda.hhs.gov[1] or (240) 402 - 4687. We also recommend that you sign up for Generic Drug e-mail updates,[2] which provide updates and information generally related to generic drug regulation.

Sincerely,

{See appended electronic signature page}

Bankim Patel, RPh
Team Leader
Division of Filing Review
Office of Regulatory Operations
Office of Generic Drugs

---

[1] A secure email address is recommended for applicants to utilize when communicating with the Agency. If you have not already established a secure email with FDA, you may send a request for a secure email address to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications. Formal regulatory submissions must be submitted according to FDA regulations and current guidances.

[2] https://updates.fda.gov/subscriptionmanagement

Bankim Patel

Digitally signed by Bankim Patel
Date: 9/24/2019 12:11:56PM
GUID: 5423006c00721f7db511c8db220bd9cf

ANDA 212340

DISCIPLINE REVIEW LETTER

Sandoz Inc.
100 College Road West
Princeton, NJ 08540
Attention: Gregory Seitz
Executive Director, Regulatory Affairs

Dear Mr. Seitz:

This communication is in reference to your abbreviated new drug application (ANDA) dated August 28, 2019, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Iron Sucrose Injection USP, 50 mg Elemental Iron/2.5 mL (20 mg/mL), 100 mg Elemental Iron/5 mL (20 mg/mL) and 200 mg Elemental Iron/10 mL (20 mg/mL) Single-Dose Vials.

We have completed the Labeling review of this ANDA and have the following preliminary thoughts on possible deficiencies:

LABELING DEFICIENCIES:

Labeling Deficiencies determined on 9/26/2019 based on your submission(s) received 8/28/2019:

1. **GENERAL COMMENTS** -
   Please comment as to whether text appears on your cap/ferrule overseal. USP standard prohibits the use of certain statements on the cap/ferrule overseal. We refer you to the following address for additional information and guidance:
   https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/genChapter1Labeling.pdf

2. **CONTAINERS** – Revise the Principle Display Panel to read as follows to be in accordance with the reference listed drug: (Below is an example for 50 mg strength, but the same format applies to all proposed strengths)

(b)(4)

3. **CARTONS** - See comments under 2. above. (Below is an example for 50 mg strength, but the same format applies to all proposed strengths/carton sizes)

4. **PRESCRIBING INFORMATION** –
How Supplied - Revise to read as follows – (Delete "FE" throughout the text)
Iron sucrose injection is supplied sterile in 2.5 mL, 5 mL, and 10 mL single-dose vials. Each 2.5 mL vial contains 50 mg elemental iron, each 5 mL vial contains 100 mg elemental iron and each 10 mL vial contains 200 mg elemental iron (20 mg/mL).

NDC 0781-3485-95	50 mg/2.5 mL Single-Dose Vial	Packages of 10
NDC 0781-3485-96	50 mg/2.5 mL Single-Dose Vial	Packages of 25
NDC 0781-3486-95	100 mg/5 mL Single-Dose Vial	Packages of 10
NDC 0781-3486-96	100 mg/5 mL Single-Dose Vial	Packages of 25
NDC 0781-3487-14	200 mg/10 mL Single-Dose Vial	Packages of 5
NDC 0781-3487-92	200 mg/10 mL Single-Dose Vial	Packages of 10

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.
It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

If you would like to respond to these possible deficiencies before the end of this review-cycle, we request a complete written response no later than November 01, 2019. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
LABELING

If you do not submit a complete written response by November 01, 2019, these possible deficiencies may be incorporated in a complete response letter.

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the GDUFA II Commitment Letter[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified as we complete our review.

If you respond to these issues during this review cycle, depending on the timing of your response, we may not be able to consider your response before taking action on your application.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions, please contact Juliette Larmie-Gyamfi, Labeling Project Manager, at Juliette.Larmie-Gyamfi@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Juliette Larmie-Gyamfi, Pharm.D.
Labeling Project Manager
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

[1] The term "GDUFA II Commitment Letter" refers to the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

U.S Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Juliette
Larmie-Gyamfi

Digitally signed by Juliette Larmie-Gyamfi
Date: 10/18/2019 11:53:42AM
GUID: 5508755d000926ebceca6d5de2d276c5

List of Deficiencies for ANDA #212340

A. Drug Substance Deficiencies

B. Drug Product Deficiencies

C. Microbiology Deficiencies

1.

2.

3.

4. (b)(4)

a)

b)

5.

(b)(4)

(b)(4)

14. (b)(4)

D. Process Deficiencies

1. (b)(4)

(b)(4)

2. (b)(4)

(b)(4)

(b)(4)

3. (b)(4)

(b)(4)

E. Facilities Deficiencies

F. Biopharmaceutics Deficiencies

ANDA 212340

INFORMATION REQUEST

Sandoz Inc
100 College Road West
Princeton, NJ 08540
Attention: Gregory Seitz
Executive Director, Regulatory Affairs

Dear Gregory Seitz:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on August 28, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Iron Sucrose Injection, USP Eq. 20 mg base/mL.

We are reviewing the Quality section of your submission and have the following comments and information requests:

A. Drug Product

1. (b)(4)

We request a prompt written response, no later than **June 8, 2020** in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an

amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY

If you have any questions, please contact Temitope Oriola, PharmD, Regulatory Business Process Manager, at Temitope.Oriola@fda.hhs.gov or (240) 402 - 4646.

Sincerely,

{See appended electronic signature page}

Temitope Oriola, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

ANDA 212340

INFORMATION REQUEST
QUALITY

Sandoz Inc
100 College Road West
Princeton, NJ 08540
Attention: Gregory Seitz
Executive Director, Regulatory Affairs

Dear Gregory Seitz:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on August 28, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Iron Sucrose Injection USP, 50 mg/2.5 mL, 100 mg/5 mL, and 200 mg/10 mL.

We also refer to your December 28, 2020 submission, containing complete response.

Reference is also made to any amendments submitted prior to the issuance of this letter.

We are reviewing the Quality section of your submission and request the following additional information/clarification and/or have the following comments:

QUALITY

A. Drug Substance

1. [Insert Comments]

B. Drug Product

1. [Insert Comments]

We request a complete written response, no later than March 6, 2023 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. If you are responding to a late cycle information request[1], the goal date may be extended based upon the major or minor deficiencies included upon receipt of the response. The goal

date assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY
MINOR

If you do not submit a complete written response by March 6, 2023, the listed information requests may be incorporated in a discipline review letter or complete response letter.

As described in FDA's draft guidance for industry *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions*, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, please contact Erin Andrews, Regulatory Business Process Manager, at erin.andrews@fda.hhs.gov or (240) 402 - 8578.

Sincerely,

{See appended electronic signature page}

Erin Andrews
Regulatory Business Process Manager
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

[1] Late cycle defined as IRs or DRLs issued after the mid-cycle of an original ANDA or less than 90 days from the goal date for any ANDA amendment.