

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208551Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approval

**NDA 208551
Review #1**

| | |
|-------------------------|------------------------------------------------------------------|
| Drug Name/Dosage Form | Triferic (Ferric Pyrophosphate Citrate)/ Powder for Hemodialysis |
| Strength | 272 mg iron (III)/ packet |
| Route of Administration | Hemodialysis (hemodialysis) |
| Rx/OTC Dispensed | Rx |
| Applicant | Rockwell Medical Inc. |
| US agent, if applicable | |

Submission History

| SUBMISSION(S) REVIEWED | DOCUMENT DATE | DISCIPLINE(S) AFFECTED |
|------------------------|-----------------|----------------------------------|
| <i>eCTD 0000</i> | <i>06/25/15</i> | <i>New NDA</i> |
| <i>eCTD 0003</i> | <i>07/15/15</i> | <i>Labeling</i> |
| <i>eCTD 0004</i> | <i>07/31/15</i> | <i>Response to IR - labeling</i> |
| <i>eCTD 0005</i> | <i>09/08/15</i> | <i>Labeling</i> |
| <i>eCTD 0008</i> | <i>10/29/15</i> | <i>CMC - microbiology</i> |
| <i>eCTD 0009</i> | <i>12/15/15</i> | <i>Response to IR - CMC</i> |
| <i>eCTD 0010</i> | <i>01/06/16</i> | <i>Labeling</i> |
| <i>eCTD 0011</i> | <i>01/27/16</i> | <i>Response to IR - CMC</i> |
| <i>eCTD 0012</i> | <i>03/14/16</i> | <i>Response to IR - CMC</i> |
| <i>eCTD 0013</i> | <i>03/16/16</i> | <i>Revised Labeling</i> |
| <i>eCTD 0014</i> | <i>03/22/16</i> | <i>Revised Labeling</i> |
| <i>eCTD 0015</i> | <i>03/28/16</i> | <i>Response to IR - CMC</i> |

Quality Review Team

| DISCIPLINE | REVIEWER | DIVISION/BRANCH |
|---------------------|----------------------|-----------------|
| Drug Substance | William Adams | DNDPI/NDPBII |
| Drug Product | William Adams | DNDPI/NDPBII |
| Process | Diane Goll | DPAI/PABII |
| Microbiology | Nandini Bhattacharya | DMA/MABII |
| Facility | Steve Hertz | DIA/IABI |
| Biopharmaceutics | Banu Zolnik | ONDP/DB/BBII |
| Regulatory Business | Rabiya Laiq | DRBPM1/RBPMBI |



QUALITY ASSESSMENT



| | | |
|----------------------------|-----------------|--------------|
| Process Manager | | |
| Application Technical Lead | William Adams | DNDPI/NDPBII |
| Laboratory (OTR) | N/A | |
| ORA Lead | Paul Perdue Jr. | DMPTPO/MDTP |
| Environmental Analysis | William Adams | DNDPI/NDPBII |

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

DMFs: None

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

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|----------|--------------------|-------------------|
| NDA | 206317 | Triferic solution |
| IND | 051290 | FPC Injection |
| IND | (b) (4) | Triferic |

2. CONSULTS: None

Executive Summary

I. Recommendations and Conclusion on Approvability

Executive Summary

NDA 208551 (Triferic powder) is the companion application with NDA 206317 (Triferic solution).

DRUG SUBSTANCE (FPC)

NDA 206317 is referenced for CMC information regarding drug substance. This application was approved for the manufacture and control of bulk FPC at (b) (4)

(b) (4) for release and stability testing. Supplement 03 to the NDA 206317, for the manufacture in (b) (4), is currently CR. Supplement 04, for (b) (4)

(b) (4) was approved 11/10/15. Supplement 05, for the manufacture in (b) (4)

(b) (4), is currently CR. Supplement 06, for multiple changes to the control site responsibilities and methods, is currently IR. With the approval of these supplements in NDA 206317, the proposed CMC changes may be approved in NDA 208551. Until that time, the CMC information approved in NDA 206317 is acceptable for use in NDA 208551.

Ferric Pyrophosphate Citrate (USAN) is an octahedral coordination complex composed of ferric ion surrounded by pyrophosphate and citrate ligands with associated sodium and sulfate ions. Active moiety is stated to be four complexes in sequence sharing pyrophosphate and citrate ligands. Molecular structure of the active moiety is established by mass spectrometry, x-ray analysis, elemental analysis and ion content. Bulk drug material is a yellow to green (b) (4) powder and very soluble in water. This material is very (b) (4)

Currently, manufacture is by (b) (4). The key steps are (b) (4). The synthesis process, process controls and material specifications are adequate for the intended purpose and described in sufficient detail. The process includes (b) (4)

(b) (4). Packaging for storage and shipment provides (b) (4). Currently manufacture and packaging is by (b) (4) with release and stability testing performed by (b) (4)

(b) (4). Testing responsibilities for each contract lab are specified. Each proposed site has been found to meet GMP standards.

The release and stability specification (tests, analytical methods and acceptance criteria) are adequate to address appearance, identity, assay, purities (b) (4) other ions and metals), residual solvents, and microbiological attributes. The proposed

analytical methods have been described in sufficient detail and validated at their site of use for their intended purpose. The proposed criteria have been justified and accepted. Appropriate reference standards have been established.

The proposed packaging system is (b) (4)

(b) (4) is justified by the stability studies. Packaging components and their acceptance specifications are described in sufficient detail and justified.

The primary stability study data and information is sufficient to support a re-test period of (b) (4) months when stored at (b) (4) in the proposed packaging system. The post approval stability protocol and commitment are acceptable.

DRUG PRODUCT (sachet)

Triferic powder is bulk FPC without excipients packaged into a packet (sachet) containing 272.0 mg Fe(III) as FPC use in the preparation of hemodialysate solution.

Sachet manufacture uses (b) (4) paper (b) (4) / aluminum foil laminate film. Filled sachets are placed into 100-count cartons. The manufacturing process and process controls are adequate for the intended purpose and described in sufficient detail. The process includes (b) (4) Manufacture and secondary packaging is by (b) (4) with release and stability testing performed by (b) (4)

(b) (4) Testing responsibilities for each testing are specified. Each proposed site has been found to meet GMP standards.

The release and stability specification (tests, analytical methods and acceptance criteria) is adequate to address appearance, identity, assay, impurities (b) (4), other ions and metal), unit dose uniformity (net weight) and microbiological attributes. The proposed analytical methods have been described in sufficient detail and validated at their site of use for their intended purpose. The proposed acceptance criteria have been justified and accepted. Appropriate reference standards have been established.

The packaging components are the sachet (b) (4) and a cardboard carton. The sachet (b) (4) Materials of composition, dimensions and acceptance specification for (b) (4) are described in sufficient detail. In-use stability studies were provided in NDA 206317.

The primary stability study data and information is sufficient to establish that drug product is stable for 12 months when stored at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (between 59°C and 86°C)[USP CRT] in the commercial sachet.

The proposed sachet, carton and package insert labels are currently being negotiated.

RECOMMENDATION

The application is recommended for APPROVAL in that complete CMC information has been provided and issues raised during the review process have been resolved.

II. Summary of Quality Assessments

A. Product Overview

Triferic powder is a packet (sachet) containing 272.0 mg Fe(III) as FPC. One packet is to be admixed into 25 gallons (94.6 liters) of commercially available LBC, then administered, via a dialysis machine (b) (4)

(b) (4), as a hemodialysate containing of 110 µg Fe(III)/L as FPC.

Triferic should not be added to the acid concentrate. Dosage of Triferic® is expressed as mg of iron(III). Hemodialysis solutions should be used within 24 hours of the preparation of the Triferic/LBC mixture. The applicant states that most U.S. dialysis centers prepare LBC mix in 50, 75 or 100 gallon increments to provide a master batch Triferic/LBC solution which is then used for multiple patient treatments.

| | |
|---------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Proposed Indication(s) including Intended Patient Population | Triferic (ferric pyrophosphate citrate; FPC) is intended for the replacement of iron to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD). Triferic is not intended for use in patients receiving peritoneal dialysis and has not been studied in patients receiving home hemodialysis. |
| Duration of Treatment | Long term |
| Maximum Daily Dose | (b) (4) FPC per treatment is the expected dose |
| Alternative Methods of Administration | None |

B. Quality Assessment Overview

Manufacture and control information approved in NDA 206317 is proposed for use in this application. Supplemental applications pending in NDA 206317 can be implemented in this application when approved. Updated CMC information is provided in this application.

C. Special Product Quality Labeling Recommendations (NDA only): None

D. Final Risk Assessment (see Attachment)

CHAPTERS: Primary Quality Assessment

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CHAPTER III: Environmental Analysis

ENVIRONMENTAL ANALYSIS

Categorical Exclusion for the environmental assessment requirement is claimed under 21 CFR 25.31(b) in that the proposed NDA increases the use of the active moiety below 1 part per billion for the estimated introduction concentration (EIC) at the point of entry into the aquatic environment.

$$\text{EIC-Aquatic} = (A)(B)(C)(D) = \text{(b) (4)} \text{ ppb}$$

where

A = (b) (4) kg/year active moiety produced for direct use based on (b) (4) gram PFC/treatment)

B = (b) (4) liters per day entering POTWs; total flow of wastewater to POTWs in the US per Table I-2, Appendix I, 2008 Clean Water Needs Survey, U.S. Environmental Protection Agency (<http://water.epa.gov/scitech/datait/databases/cwns/upload/cwns2008rtc.pdf>)

C = year/365 days

D = 10^9 $\mu\text{g}/\text{kg}$ (conversion factor)

Reviewer's Assessment:

The request for categorical exclusion is granted in that the calculated EIC meets the CFR requirement.

Primary EA Reviewer:

William M. Adams
CMC Reviewer in OPQ/ONDP/DNDP1/Branch2
24 March 2016

Secondary Reviewer (and Secondary Summary, as needed):

I concur
Anamitro Banerjee
Acting Branch Chief, OPQ/ONDP/DNDP1/Branch 2
March 24, 2016

CHAPTER IV: Labeling

LABELING

1.14 Labeling

**Response dated 10/30/14 to IR letter to NDA 206317 dated 10/23/14
Amendment S-009**

Comment 1: We are concerned that the dosing instruction you have proposed in the draft label for Triferic, namely, (b) (4)

may not be applicable or sufficiently informative to the broad population of U.S. hemodialysis centers and facilities.

To support the broad applicability and utility of the proposed dosing instructions, please provide information and discussion of current materials, practice and procedures used for preparation of hemodialysis solutions in current U.S. practice and any other relevant information or data, including clinical experience you may have had using Triferic with various dialysate proportioning ratios.

Please identify the maximum hold time for the bicarbonate Triferic mixture, and how the in-use study supports this.

Response 1

(b) (4)

Amendment S-004

07/31/15 Response to IR letter dated 07/30/15 to NDA 208551.

Comment: Regarding Triferic/NDA 208551, do you intend to have this proposed formulation (powder packet) and the current Triferic formulation (solution in ampules) on the market simultaneously or will this new formulation replace the original?

If both formulations will be on the market, how do you plan to prevent confusion between the two formulations?

Response

The proposed powder packet and the currently approved 5cc ampule will be on the market at the same time. (b) (4)

(b) (4)

PACKAGE INSERT**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use TRIFERIC safely and effectively. See full prescribing information for TRIFERIC.

TRIFERIC[®] (ferric pyrophosphate citrate) solution, for hemodialysis use
TRIFERIC[®] (ferric pyrophosphate citrate) for solution, for hemodialysis use
Initial U.S. Approval: 2015

-----INDICATIONS AND USAGE-----

TRIFERIC is an iron replacement product indicated for the replacement of iron to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD). (1)

Limitation of Use

Triferic is not intended for use in patients receiving peritoneal dialysis. (1.1)
Triferic has not been studied in patients receiving home hemodialysis (1.1)

-----DOSAGE AND ADMINISTRATION-----

- * Add one 5 mL Triferic ampule to 2.5 gallons of bicarbonate concentrate to achieve a final concentration of Triferic iron (III) in the final hemodialysate of 2 micromolar (110 mcg/L). (2.1)
- * Add one 50 mL ampule of Triferic to each 25 gallons of bicarbonate concentrate to achieve a final concentration of Triferic iron (III) in the final hemodialysate of 2 micromolar (110 mcg/L). (2.1)
- * Add one packet of Triferic powder to each 25 gallons of bicarbonate concentrate to achieve a final concentration of Triferic iron (III) in the final hemodialysate of 2 micromolar (110 mcg/L). (2.1)

-----DOSAGE FORMS AND STRENGTHS-----

27.2 mg of iron (III) per 5 mL ampule (5.44 mg of iron (III) per mL). (3)
272 mg of iron (III) per 50 mL ampule (5.44 mg of iron (III) per mL). (3)
272 mg iron (III) per powder packet. (3)

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Triferic is an iron replacement product indicated for the replacement of iron to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD).

1.1 Limitation of Use

Triferic is not intended for use in patients receiving peritoneal dialysis.
Triferic has not been studied in patients receiving home hemodialysis.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

Inspect Triferic solution in ampules for signs of precipitation prior to mixing with the bicarbonate concentrate. Triferic solution should appear slightly yellow-green in color.

Triferic powder should only be added to the bicarbonate concentrate and should NOT be added to acid concentrate mixtures.

Add Triferic powder or solution to bicarbonate concentrate used for generation of hemodialysate. The concentration of Triferic iron (III) in the final hemodialysate is 2 micromolar (110 mcg/L).

(b) (4)

* Add one 5 mL (b) (4) to 2.5 gallons (9.46 liters) of bicarbonate concentrate. Multiple 5 mL Triferic ampules can be added to the master bicarbonate mix at each center at a ratio of one 5 mL ampule to each 2.5 gallons (9.46 liters) of bicarbonate concentrate.

* Add one 50 mL (b) (4) to each 25 gallons (94.6 liters) of master bicarbonate mix at each center at a ratio of one 50 mL ampule for each 25 gallons (94.6 liters) of bicarbonate concentrate.

Administer Triferic to patients at each dialysis procedure for as long as patients are receiving maintenance hemodialysis therapy for CKD.

The dosage of Triferic (b) (4) is expressed as mg of iron (III). (b) (4)

Hemodialysis bicarbonate solutions should be used within 24 hours of the preparation of the bicarbonate concentrate mixture.

3 DOSAGE FORMS AND STRENGTHS

Each Triferic Powder (b) (4) 272 mg iron (III).

Each 5 mL (b) (4) ampule contains (b) (4) (5.44 mg of iron (III) per mL).

Each 50 mL (b) (4) ampule contains (b) (4) (5.44 mg of iron (III) per mL).

11 DESCRIPTION

Triferic (ferric pyrophosphate citrate) is a mixed-ligand iron complex in which iron (III) is bound to pyrophosphate and citrate. It has a molecular formula of $\text{Fe}_4(\text{C}_6\text{H}_4\text{O}_7)_3(\text{H}_2\text{P}_2\text{O}_7)_2(\text{P}_2\text{O}_7)$ and a relative molecular weight of approximately 1313 daltons. Triferic contains iron (7.5-9.0% w/w), citrate (15-22% w/w), pyrophosphate (15-22% w/w), phosphate (< 2% w/w), sodium (18-25% w/w) and sulfate (20-35%). Ferric pyrophosphate citrate has the following molecular structure:

[molecular structure]n

Triferic Powder Packets:

(b) (4) a slightly yellow-green powder, packaged in paper, polyethylene and aluminum foil packets, each containing 272.0 mg of iron (III). (b) (4)

Triferic Solution:

(b) (4) a clear, slightly yellow-green color sterile solution containing 27.2 mg of iron (III) per 5 mL (b) (4) filled into a 5 mL or 272 mg of iron (III) per 50 mL (b) (4) filled into a 50 mL low density polyethylene (b) (4) ampule. (b) (4)

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Triferic is available in ampules or packets in the following package sizes:

| NDC Code | Package Description | Amount/Total Volume (per ampule) |
|------------------|------------------------|---------------------------------------------------------|
| | 5 mL Ampule | 27.2 mg iron (III)/ 5 mL (5.44 mg of iron (III) per mL) |
| NDC 57278-314-01 | 5 ampules per Pouch | |
| NDC 57278-314-02 | 8 Pouches per Carton | |
| | | |
| NDC 57278-316-01 | 50 mL Ampule | 272 mg iron (III)/ 50 mL (5.44 mg of iron (III) per mL) |
| NDC 57278-316-02 | 4 Ampules per Pouch | |
| NDC 57278-316-03 | 6 Pouches per Carton | |
| | | |
| NDC Code | Package Description | Amount/Package |
| NDC 57278-315-01 | Packet | 272 mg iron (III)/packet |
| NDC 57278-315-02 | 100 Packets per Carton | |

16.2 Storage

Store **ampules** protected from light in the aluminum pouch at controlled room temperature (20° to 25°C [68° to 77°F]); excursions permitted to 15°-30°C (59° to 86°F) [See USP Controlled Room Temperature].

Store **packets** at controlled room temperature (20° to 25°C [68° to 77°F]); excursions permitted to 15°-30°C (59° to 86°F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Prior to the administration of Triferic:

- * Question patients regarding any prior history of reactions to parenteral iron products.
- * Advise patients of the risks associated with Triferic.
- * Advise patient to report any signs and symptoms of hypersensitivity that may develop during and after the dialysis session, such as rash, itching, dizziness, lightheadedness, swelling and breathing problems [see Warnings and Precautions (5)].

Manufactured for
Rockwell Medical, Inc.

Wixom, MI 48393

Reviewer's Assessment:

Discussion

NDA 206317 is for *Triferic Solution*, 5mL of a sterile solution packaged in a (b) (4) ampule containing 5.44 mg Fe(III)/mL as FPC in Water for Injection, USP. One ampule is to be admixed into 2.5 gallons LBC at the clinic, then administered, via a dialysis machine (b) (4) as a hemodialysate containing of 110 µg Fe(III)/L as FPC. NDA 206317/suppl-02 approved the use of a 50cc (b) (4) ampule containing 50 mL of the same solution. The 50cc ampule is intended to be admixed with 25 gallons in LBC and administered in the same manner as the 5cc ampule.

NDA 208551 is for *Triferic Powder*, bulk FPC (DS) packaged into a paper (b) (4)/aluminum foil laminate packet (sachet) containing 272.0 mg Fe(III) as FPC with no excipients. One packet is intended to be admixed into 25 gallons of LBC, then administered in the same manner as *Triferic Solution*.

The applicant states that most U.S. dialysis centers prepare LBC mix in 50, 75 or 100 gallon increments to provide a master batch *Triferic/LBC* solution which is then used for multiple patient treatments.

Response 1: This information has been incorporate into the package insert. The NDA notes that the master batch mix (*Triferic/LBC*) is prepared and a portion is delivered to the dialysis mixing machine.

S-004 Response: (b) (4)

Highlights

Indication & Usage: Acceptable

Dosage & Administration: Revisions in amendment S-013 are acceptable.

Full Prescribing Information

Section 1: Revisions in amendment S-013 are acceptable and DMEPA made no comment on the retained statement "iron replacement product indicated for ...".

Section 2.1: Revisions in amendment S-013 are acceptable.

Section 3: Revisions in amendment S-013 are acceptable.

Section 11: Statements are acceptable.

Section 16.1: Revisions in amendment S-013 are acceptable. The absence of a separate NDC for individual 5cc ampules is acceptable to DMEPA (amendment S-015).

Section 16.2: Storage statement is supported by the study data in NDA sections 3.2.S.7 and 3.2.P.8.

Mfg For: Accepted in that this is the NDA holder.

DESCRIPTION section

Is the information accurate? Yes

Is the drug product subject of a USP monograph? No

HOW SUPPLIED section

- i) Is the information accurate? Yes
- ii) Are the storage conditions acceptable? Yes

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

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? Addressed in NDA 206317

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer:

Clarity and consistency of statements; see comments above.

List of Deficiencies: None

Primary Drug Product Reviewer:

William M. Adams
CMC Reviewer in OPQ/ONDP/DNDP1/Branch1
23 March 2016

Secondary Drug Product Reviewer Name and Date:

I concur.

Anamitro Banerjee
Acting Branch Chief, OPQ/ONDP/DNDP1/Branch2
March 24, 2016

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CHAPTER V: Process

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CHAPTER VI: Facilities

FACILITIES

Product Background: Triferic (ferric pyrophosphate citrate, FPC) is an iron replacement product, delivered via dialysate, to replace the iron losses in Stage 5 chronic kidney disease patients receiving maintenance hemodialysis.

NDA: 208551

Drug Product Name / Strength: 272 mg iron(III) packet

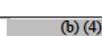
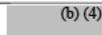
Route of Administration: Hemodialysis

Applicant Name: Rockwell Medical Inc.

3.2.S.2 Manufacture

Summary of Facility Information:

| Establishment Name | FEI Number | Responsibilities and Profile Codes | Initial Risks Identified | Current Status | Final Recommendation |
|--------------------|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|---------------------------------------------------------|----------------------------------------------------------|
| (b) (4) | (b) (4) | (b) (4) <ul style="list-style-type: none"> • API Manufacture • Bulk API Packaging • Release Testing • Stability Testing • (b) (4) (b) (4) of API prior shipping to primary packaging site • Appearance | Low risk | PAI waived because of site history and low risk process | Acceptable based on manufacturing and compliance history |

| | | | | | |
|---------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|---------------------------------------------------------|----------------------------------------------------------|
| | | <ul style="list-style-type: none"> • Identification • Assay • Solubility •  (b) (4) • Residual Solvents | | | |
|  (b) (4) |  (b) (4) |  (b) (4) <ul style="list-style-type: none"> • API Manufacture • Bulk API Packaging • Release Testing • Stability Testing | Low risk | PAI waived because of site history and low risk process | Acceptable based on manufacturing and compliance history |
|  (b) (4) |  (b) (4) | CTL  (b) (4)  of API prior shipping to primary packaging site <ul style="list-style-type: none"> •  (b) (4) • Microbial Limit Tests (MLT) • Endotoxins • Heavy Metals | Low risk | PAI waived because of site history and low risk process | Acceptable based on manufacturing and compliance history |
|  (b) (4) |  (b) (4) | CTL | Low risk | PAI waived because of | Acceptable based on manufacturing and |

| | | | | | |
|---------|--|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|-----------------------------------|--------------------|
| (b) (4) | | <ul style="list-style-type: none"> (b) (4) of API prior shipping to primary packaging site (b) (4) Microbial Limit Tests (MLT) Endotoxins Heavy Metals | | site history and low risk process | compliance history |
|---------|--|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|-----------------------------------|--------------------|

Reviewer's Assessment:

| Facility Name | FEI | Profile Code | Responsibilities | Facility Sub-Score | Process Sub-Score | Product Sub-Score | Overall Initial Facility Risk Assessment |
|---------------|---------|--------------|---------------------------------------------------------------------------------|--------------------|-------------------|-------------------|------------------------------------------|
| (b) (4) | (b) (4) | (b) (4) | Drug substance manufacturing, bulk API packaging, release and stability testing | Low | Low | Low | Low |
| (b) (4) | (b) (4) | (b) (4) | Drug substance manufacturing, bulk API packaging, release and stability testing | Low | Low | Low | Low |
| (b) (4) | (b) (4) | CTL | Analytical testing | Low | Low | Low | Low |
| (b) (4) | (b) (4) | CTL | Analytical testing | Low | Low | Low | Low |

- The (b) (4) facility performs drug substance manufacturing, bulk API packaging, and release and stability testing (including appearance, identification, assay, solubility, (b) (4) and residual solvents). Additionally, this facility performs (b) (4) of API

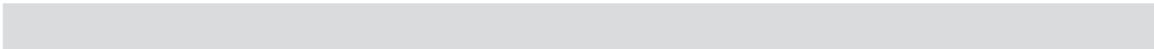
prior shipping to primary packaging site. This facility was inspected on 6/27/14 for profile (b) (4) and was classified NAI. This inspection (06/23-27/2014) provided coverage to the quality, facilities and equipment and production systems for the cGMP portion of the inspection. The pre-approval inspection for drug substance, Soluble Ferric Pyrophosphate (NDA-206317) covered three objectives: Readiness for commercial manufacturing, data integrity and conformance to application. Examples of documents reviewed during this inspection include, but were not limited to, deviations, change controls, batch records, process validation records, cleaning records for bioreactors, equipment calibration records and supplier qualification documents. No FDA-483 were issued. However, the following items were verbally communicated to the management present: 1) Unidentified peaks and shifts in retention time observed during validation or routine release testing should be addressed; and 2) corrective and preventative actions for deviation investigation need to be adequate. Ms. Simona Merica, Director, Quality and Regulatory Affairs promised correction to the above discussion items. An approval recommendation for on-site activities related to NDA-206317 was given at the close of the inspection. The OPF facilities reviewer made an acceptable recommendation based on district recommendation (file review).

NDA 208551 Triferic (ferric pyrophosphate citrate, FPC) is an iron replacement product, delivered via dialysate, to replace the iron losses in Stage 5 chronic kidney disease patients receiving maintenance hemodialysis. Triferic meets the unmet need for an iron replacement product that effectively treats the functional iron deficiency in these patients without increasing iron stores. Triferic received FDA approval on January 23, 2015, NDA 206317. The presentation approved on January 23, 2015 was a 5 mL ampule containing 27.2 mg iron to be added to 2.5 gallon of liquid bicarbonate concentrate yielding a final iron concentration of 2 μM (110 $\mu\text{g/L}$) in the final dialysate. Rockwell Medical intends to commercialize a Triferic packet containing only API powder, for dilution into 25 gallons of liquid bicarbonate concentrate. The API powder in the new packaging conformation (b) (4), not containing any excipients. Since the API manufacturing process (b) (4) the pre-approval inspection results (b) (4) can be used for the overall facilities recommendation.

- The (b) (4) facility also performs drug substance manufacturing, bulk API packaging, and release and stability testing. This facility was inspected on (b) (4) for PAC 46832 (PAI) and was classified NAI. This facility was also inspected on (b) (4) for PAC 56002 (GMP) and was also classified NAI. Both inspections covered the quality, laboratory, materials,

production, facilities and equipment, and packaging and labeling systems. The OPF facilities reviewer made an acceptable recommendation based on profile.

- The (b) (4) facility performs (b) (4) of API prior shipping to primary packaging site, as well as analytical testing (including (b) (4) microbial limit tests (MLT), endotoxins, and heavy metals). This facility was inspected on (b) (4) for PAC 46832 (PAI) and was classified NAI. This facility was also inspected on (b) (4) for PAC 56002 (GMP) and was also classified NAI. Both inspections covered the quality and laboratory systems. The OPF facilities reviewer made an acceptable recommendation based on profile.
- The (b) (4) facility performs (b) (4) of API prior shipping to primary packaging site, as well as analytical testing (including (b) (4), microbial limit tests (MLT), endotoxins, and heavy metals). This facility was inspected on (b) (4) for profile CTL and was classified NAI. This inspection covered the quality and laboratory systems. The OPF facilities reviewer made an acceptable recommendation based on profile.
- As this drug substance process has already been evaluated and approved in NDA 206317, the process and product risk sub-scores in the facilities initial quality assessment is low.



3.2.P.3 Manufacture

Summary of Facility Information:

| Establishment Name | FEI Number | Responsibilities and Profile Codes | Initial Risks Identified | Current Status | Final Recommendation |
|--------------------|------------|------------------------------------------------------------------------------------------------------------|--------------------------|-------------------------------------------------|----------------------------------------------------------|
| (b) (4) | (b) (4) | POW <ul style="list-style-type: none"> • Primary/secondary packaging • Labeling | Low risk | PAI waived because of site history and low risk | Acceptable based on manufacturing and compliance history |

| | | | | | |
|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|---------------------------------------------------------|----------------------------------------------------------|
| | (b) (4) | | | process | |
|  | | <p>CTL</p> <ul style="list-style-type: none"> • Release and stability testing <ul style="list-style-type: none"> • Appearance • Identification • Assay • Solubility •  (b) (4) •  (b) (4) • Microbial Limit Tests (MLT) • Endotoxins • Heavy Metals • Net Weight | Low risk | PAI waived because of site history and low risk process | Acceptable based on manufacturing and compliance history |
|  |  (b) (4) | <p>CTL</p> <ul style="list-style-type: none"> • Release and stability testing <ul style="list-style-type: none"> • Appearance • Identification • Assay • Solubility •  (b) (4) | Low risk | PAI waived because of site history and low risk process | Acceptable based on manufacturing and compliance history |

| | | | | | |
|---------|---------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|---------------------------------------------------------|----------------------------------------------------------|
| | | <p>(b) (4)</p> <ul style="list-style-type: none"> • (b) (4) • Microbial Limit Tests (MLT) • Heavy Metals • Net Weight | | | |
| (b) (4) | (b) (4) | <p>CTL</p> <ul style="list-style-type: none"> • Release and stability testing <ul style="list-style-type: none"> • Appearance • Identification • Assay • Solubility • (b) (4) | Low risk | PAI waived because of site history and low risk process | Acceptable based on manufacturing and compliance history |

Reviewer's Assessment:

| Facility Name | FEI | Profile Code | Responsibilities | Facility Sub-Score | Process Sub-Score | Product Sub-Score | Overall Initial Facility Risk Assessment |
|---------------|---------|--------------|------------------------------------------|--------------------|-------------------|-------------------|------------------------------------------|
| (b) (4) | (b) (4) | POW | Primary/secondary packaging and labeling | Low | Low | Low | Low |
| | | CTL | Release and stability testing | Low | Low | Low | Low |
| | | CTL | Release and stability testing | Low | Low | Low | Low |
| | | CTL | Release and stability testing | Low | Low | Low | Low |

- The (b) (4) facility performs drug product primary/secondary packaging and labeling. This facility was inspected on (b) (4) for profile POW and was classified VAI. This inspection covered drug packaging operations including Quality, Materials, Facilities and Equipment, and Packaging and Labeling Systems, as well as the manufacture and packaging of dietary supplements, and resulted in the issuance of a 5-point FDA 483 for the following: (b) (4)

(b) (4)

(b) (4) The OPF facilities reviewer requested a domestic district file review to determine if the firm's actions to the inspectional observations were adequate. The district made an acceptable recommendation based on file review. The OPF facilities reviewer made an acceptable recommendation based on district recommendation.

NDA 208551 Triferic (ferric pyrophosphate citrate, FPC) is an iron replacement product, delivered via dialysate, to replace the iron losses in Stage 5 chronic kidney disease patients receiving maintenance hemodialysis. Triferic meets the unmet need for an iron replacement product that effectively treats the functional iron deficiency in these patients without increasing iron stores. Triferic received FDA approval on January 23, 2015, NDA 206317. The presentation approved on January 23, 2015 was a 5 mL ampule containing 27.2 mg iron to be added to 2.5 gallon of liquid bicarbonate concentrate yielding a final iron concentration of 2 μM (110 $\mu\text{g/L}$) in the final dialysate. Rockwell Medical intends to commercialize a Triferic packet containing only API powder, for dilution into 25 gallons of liquid bicarbonate concentrate. The API powder in the new packaging conformation [REDACTED] (b) (4). Since the API manufacturing process [REDACTED] (b) (4) the pre-approval inspection results of [REDACTED] (b) (4) can be used for the overall facilities recommendation. There is no additional drug product manufacturing of the API, as it is only packaged and labeled for NDA 208551.

- The [REDACTED] (b) (4) facility performs release and stability testing (including appearance, identification, assay, solubility, [REDACTED] (b) (4) microbial limit tests (MLT), endotoxins, heavy metals, and net weight). This facility was inspected on [REDACTED] (b) (4) for PAC 46832 (PAI) and was classified NAI. This facility was also inspected on [REDACTED] (b) (4) for PAC 56002 (GMP) and was also classified NAI. Both inspections covered the quality and laboratory systems. The OPF facilities reviewer made an acceptable recommendation based on profile.
- The [REDACTED] (b) (4) facility performs release and stability testing (including appearance, identification, assay, solubility, [REDACTED] (b) (4) microbial limit tests (MLT), heavy metals, and net weight). This facility was inspected on [REDACTED] (b) (4) for profile CTL and was classified NAI. This inspection covered the quality and laboratory systems. The OPF facilities reviewer made an acceptable recommendation based on profile.
- The [REDACTED] (b) (4) facility performed release and stability testing (including appearance, identification, assay, solubility, and [REDACTED] (b) (4) for registration batches. In addition to the inspection reference in the drug substance manufacturer section, the facility has an acceptable compliance status for profile CTL. The OPF facilities reviewer made an acceptable recommendation based on district recommendation (file review).

- As this drug substance process has already been evaluated and approved in NDA 206317, the process and product risk sub-scores in the facilities initial quality assessment was deemed low.

Comparability Protocols**Reviewer's Assessment: N/A****Post-Approval Commitments****Reviewer's Assessment: N/A****Lifecycle Management Considerations****N/A****List of Deficiencies: N/A****Primary Facilities Reviewer Name and Date:****The overall manufacturing inspection recommendation is acceptable.**

Steven Hertz
Consumer Safety Officer
OPF Division of Inspectional Assessment, Branch 1
3/20/16

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

I concur that the overall manufacturing inspection recommendation for the subject NDA is acceptable.

Steven Fong, Ph.D.
Microbiologist
OPF Division of Inspectional Assessment, Branch 1
3/21/2016

CHAPTER VII: Biopharmaceutics

BIOPHARMACEUTICS**Product Background:**

NDA 208551 (Triferic powder) is the companion application with the approved NDA 206317 (Triferic solution). The proposed drug product has the same indication as Triferic solution.

Drug Product Name / Strength: Triferic (Ferric Pyrophosphate Citrate)/ Powder for Hemodialysis

Route of Administration:

The proposed drug product contains 272 mg iron (III) per packet is added to 25 gallons of liquid bicarbonate which equals to 27.2 mg of iron per 2.5 gallons of liquid bicarbonate concentrate and delivers to patients a final dose of 2 μ M iron (110 μ g/L) via hemodialysate.

Applicant Name: Rockwell Medical

Review Summary:

The proposed drug product in powder forms a solution upon mixing with the liquid bicarbonate. The Applicant is cross referencing the PK studies to NDA 206317, therefore biowaiver is not needed. There are no biopharmaceutics data or information in this NDA to be assessed.

Primary Biopharmaceutics Reviewer:

Since there are no biopharmaceutics data or information to be reviewed in this NDA, the Division of Biopharmaceutics defers the approvability decision to the other review disciplines.

3/21/16

Banu Sizanli Zolnik, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products/OPQ

Secondary Reviewer:

I concur with Dr. Zolnik that the approvability decision on NDA 208551 be deferred to the other review disciplines.

3/21/2016

Okpo Eradiri, Ph.D.
Biopharmaceutics Lead (acting)
Division of Biopharmaceutics
Office of New Drug Products/OPQ

CHAPTER VIII: Microbiology

MICROBIOLOGY

Product Background:

NDA: 208551

Drug Product Name / Strength: Triferic / 272 mg iron (iii) in (b) (4) paper/ (b) (4) aluminum foil laminate (b) (4) packets/ (b) (4) used for admix with liquid bicarbonate concentrate during hemodialysis

Route of Administration: used for admix during hemodialysis

Applicant Name: Rockwell Medical Inc.

Manufacturing Site: (b) (4)

Method of Sterilization: N/A; The drug product is a (b) (4) powder

Review Summary: The overall manufacturing controls are adequate and the drug product is packaged into (b) (4) packets using (b) (4). The proposed compendial release tests and specifications are appropriate and have been verified suitable for use with the subject drug product. The final drug product specification has appropriate microbial limits and the reviewer anticipates that there is no risk for microbial proliferation during storage of the powdered drug substance or manufacture/filling of the drug product. During patient administration, the (b) (4) drug product powder is added to (b) (4) bicarbonate dialysis concentrate and the hemodialysis bicarbonate solution can be held for NMT 24 hours since preparation. Hold time studies for up to (b) (4) following addition of the soluble ferric pyrophosphate (SFP) in the bicarbonate solution were performed to demonstrate that the ANSI/AAMI/ISO (b) (4) action levels for dialysate bioburden and endotoxins of (b) (4) CFU/mL and (b) (4) EU/mL, respectively, were met.

List Submissions being reviewed (table):

| Submit | Received | Review Request | Assigned to Reviewer |
|----------|----------|----------------|----------------------|
| 6/25/15 | 6/25/15 | 7/9/15 | 7/10/15 |
| 10/29/15 | 10/29/15 | | 10/29/15 |
| 12/15/15 | 12/15/15 | | 12/15/15 |

Highlight Key Outstanding Issues from Last Cycle: Gratuitous information relevant to product quality microbiology review was submitted on 10/29/15. An Agency IR with

microbiology deficiencies was conveyed to the sponsor on 11/19/15. The sponsor responded on 12/15/15. The responses are incorporated in this review.

Concise Description Outstanding Issues Remaining: N/A. This Microbiology Product Quality review is recommended from a sterility assurance standpoint.

S Drug Substance

The drug substance is a (b)(4) yellow to green powder and is obtained from (b)(4). The manufacture of this (b)(4) powder is not reviewed here.

Note to reviewer: The incoming drug substance release and stability testing is performed at (b)(4). Since SFP is formulated into a dialysis solution, the amount of Total Aerobic Count, Total Molds and Yeast, and Bacterial Endotoxins are controlled in the drug substance. The API specifications have been set at (b)(4) CFU/g for the Total Aerobic Count, (b)(4) CFU/g for the Total Molds and Yeasts and at (b)(4) EU/mg for Bacterial Endotoxins (Module 3.2.S.4.1). In addition, final drug product specification has appropriate microbial limits and the reviewer anticipates that there is no risk for microbial proliferation during storage of the powdered drug substance or manufacture/filling of the drug product. The (b)(4) approved drug product in NDA 206317 (reviews N206317R1 by N. Sweeney for soluble ferric pyrophosphate concentrate solution (5.44 mg Fe/mL) in 5 mL single use LDPE (b)(4) ampoules and 206317s2.doc, dated 6/27/15 by Y. Smith for soluble ferric pyrophosphate concentrate solution 272 mg Triferic in WFI at a concentration of 5.44 mg Fe/mL in 50 mL LDPE (b)(4) (b)(4) ampoule size).

Reviewer’s Assessment: Acceptable

The provided acceptance criteria comply with those specified by USP (b)(4) substances for pharmaceutical use.

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – The drug product is a (b)(4) yellow to green powder packaged in (b)(4) packets, for dilution into 25 gallons of liquid bicarbonate concentrate.
- **Drug product composition** –
Table 1- Composition of the FPC Drug product (Sponsor Table 1 Module 3.2.P.1.1)

| Ingredients | Function | Quality | Unit composition |
|-------------|----------|---------|------------------|
|-------------|----------|---------|------------------|

| | | standard | quantity | percent |
|-----------------------------------------------------|--------------------|--------------------|-----------------|---------------------------|
| Drug substance Ferric Pyrophosphate Citrate (FPC)\$ | Active ingredient* | Reference standard | 272 mg Fe (w/w) | 7.5-9.0% (w/w) (b) (4) |
| Total | | | (b) (4) g | (b) (4) % |

* The approved dosage form of FPC (Triferic) FPC Solution for NDA 206317 for administration by hemodialysis, is a clear, green or greenish-yellow sterile solution containing 5.44 mg Fe/mL in water (Water for Injection, USP), which is admixed with liquid bicarbonate concentrate (2.5 gal) on-site at the clinic (b) (4), to yield a hemodialysate containing iron (as FPC) at a concentration of 110 µg Fe/L. The sponsor wanted to market the drug substance FPC as a powder to be added to the master bicarbonate concentrate mix at the dialysis center for (b) (4) preparation. It is indicated that the FPC will be used during hemodialysis in the same manner as the approved Triferic concentrate solution.

\$Changed to FPC from SFP in line with the approved USAN name (indicated in reviewer’s guide).

- **Description of container closure system** – The drug product is supplied in paper/ (b) (4) aluminum foil laminate packet supplied by (b) (4)

Reviewer’s Assessment: Acceptable

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

P.2.5 Microbiological Attributes

- **Container-Closure and Package integrity** – The details of a (b) (4) test performed as an in process control during (b) (4) is not provided. The drug product is a (b) (4) powder no additional information is requested for c/c integrity.
- **Preservative Effectiveness** – The drug product is a (b) (4) powder, that does not contain any preservative and is packaged into (b) (4) (where the contents of the entire packet is added to the diluent) (b) (4) packets. No information on antimicrobial effectiveness testing (AET) studies is required.
- **Justification for not having a microbial limit specification for a non-**

sterile drug product – The finished drug product has a microbial limit specification. See Section P.5.1

Reviewer's Assessment: Acceptable

The provided acceptance criteria for microbial limits comply with those specified by USP (b) (4) substances for pharmaceutical use. The sponsor has submitted adequate data to validate the test in Section P.3.5. C/C integrity is assessed by (b) (4) test as an in-process control and the provided test method is acceptable for the (b) (4) powder dosage form supplied in paper/foil laminate packets.

P.3 Manufacture

P.3.1 Manufacturers

Manufacture and release testing will occur at the following location:

(b) (4) API prior to shipping at the primary packaging suite, release and stability testing and release of API occur at:

(b) (4)

Primary and secondary packaging in (b) (4) packets and labeling occur at:

(b) (4)

Release and stability testing (including microbial limits testing, endotoxins testing) and release of final product occur at:

(b) (4)

P. 3.3 Description of the Manufacturing Process and Process Controls

(b) (4)

ANSI/AAMI/ISO 11663 action levels for dialysate bioburden and endotoxin ((b) (4) CFU/mL and (b) (4) EU/ml, respectively)

The overall manufacturing controls described in the submission are adequate to minimize patient risk. The proposed compendial release tests and specifications are appropriate and method suitability has been verified for the (b) (4) drug product. The labeling limits the post-dilution hold times and the proposed storage instructions comply with the ANSI/AAMI/ISO (b) (4). The product quality microbiology review is recommended.

Primary Microbiology Reviewer Name and Date:

Nandini Bhattacharya, Ph.D.

Microbiologist

CDER/OPF/DMA/BRANCH II

3.11.2016

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

Bryan S. Riley, Ph.D.

Branch Chief

CDER/OPQ/OPF/DMA/Branch II

3/24/2016

CHAPTER IX: Additional Quality Discipline

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Substance

| From Initial Risk Identification | | | Review Assessment | | |
|----------------------------------|------------------------------------|-------------------------|-------------------------------------------------------------------|--------------------------|------------------------------------------|
| Attribute/ CQA | Factors that can impact the CQA | Initial Risk Ranking | Risk Mitigation Approach | Final Risk Evaluation | Lifecycle Considerations/ Comments |
| Appearance (color) | (b) (4) | L | (b) (4) during manufacture & packaging | L | None |
| Total Iron Content | Incomplete synthesis reaction | L | Well defined manufacturing process | L | None |
| Anion Content | * Incomplete synthesis reaction | * M | * Well defined manufacturing process | * L | * None |
| | * Product degradation | * M | (b) (4) during manufacture | * L | * None |
| Process Impurities | Incomplete synthesis reaction | L | * Well defined manufacturing process | L | None |
| (b) (4) | Product degradation | L | Well defined manufacturing process | L | None |
| (b) (4) | (b) (4) | M | Well defined manufacturing process and IPCs | L | None |
| Residual (b) (4) | (b) (4) | M | Well defined manufacturing process and IPCs | L | None |
| Residual Metals | Poor quality reagents | L | Appropriate starting material and reagent specifications | L | None |
| Microbial Limits Test | Excess bioburden (b) (4) | L | Appropriate specification (b) (4) | L | None |
| Bacterial Endotoxins | Excess endotoxin (b) (4) | L | Appropriate specification (b) (4) | L | None |

b) Drug Product

| From Initial Risk Identification | | | Review Assessment | | |
|----------------------------------|------------------|--------------|-------------------|------------|-----------|
| Attribute/ | Factors that can | Initial Risk | Risk Mitigation | Final Risk | Lifecycle |

| CQA | impact the CQA | Ranking | Approach | Evaluation | Considerations/ Comments |
|-------------------------------|-----------------------------------|---------|---------------------------------|------------|-----------------------------|
| Appearance (color)/Solubility | (b) (4) | M | (b) (4) | L | None |
| Total Iron Content | DS degradation during (b) (4) | L | (b) (4) | L | None |
| Anion Content | DS degradation during (b) (4) | M | (b) (4) | * L | * None |
| Process Impurities | DS degradation during (b) (4) | L | Appropriate DS specification | L | None |
| (b) (4) | DS degradation during (b) (4) | L | Appropriate DS specification | L | None |
| (b) (4) | (b) (4) | M | (b) (4) | L | None |
| Net Weight | Inappropriate IPC for fill weight | M | Appropriate IPC for fill weight | L | None |
| Residual Metals | Poor quality bulk DS | L | Appropriate DS specifications | L | None |
| Microbial Limits Test | Excess bioburden level in bulk DS | L | Appropriate DS specification | L | None |
| Bacterial Endotoxins | Excess endotoxin level in bulk DS | L | Appropriate DS specification | L | None |
| DS Particle Size | (b) (4) | M | Appropriate (b) (4) | L | None |

ATTACHMENT II: List of Deficiencies for Complete Response

- A. Drug Substance Deficiencies:** None
- B. Drug Product Deficiencies:** None
- C. Environmental Analysis Deficiencies:** None
- D. Labeling Deficiencies:** None
- E. Process Deficiencies**

(b) (4)

Process Deficiency #2 (R2)

(b) (4)

F. Facilities Deficiencies: None

G. Biopharmaceutics Deficiencies: None

H. Microbiology Deficiencies: None

OVERALL ASSESSMENT AND SIGNATURES:***Application Technical Lead:***

**William M.
Adams -S**

Digitally signed by William M. Adams -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300006782,
cn=William M. Adams -S
Date: 2016.03.29 14:08:17 -04'00'

William M. Adams
CMC Reviewer in OPQ/ONDP/DNDP1/Branch2
24 March 2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO: William Adams, CMC Reviewer
Olen Stephens, Branch Chief
Rabiya Laiq, MVP Chief
Office of (OMPT/CDER/OPQ/ONDP/DNDPI/NDPBII)
E-mail Address: @fda.hhs.gov
Phone: (301)-796-1321

FROM: FDA
Division of Pharmaceutical Analysis (CDER/OPQ/OTR/DPA)
Michael E. Hadwiger, MVP Coordinator
645 S Newstead Avenue
St. Louis, MO 63110
Phone: (314) 539-3811

Through: Michael Trehy, Lab Chief, Branch 2, (CDER/OPQ/OTR/DPA)
Phone: (314) 539-3815

SUBJECT: Methods Validation Report Summary

Application Number: 208551

Name of Product: Triferic

Applicant: Rockwell Medical Inc

Applicant's Contact Person: Raymond Pratt, MD

Address: 30142 S. Wixom Road, Wixom, MI 48393

Telephone: 248 960 9009

Email: rpratt@rockwellmed.com

Date Methods Validation Consult Request Form Received by DPA: 9/4/2015

Date Methods Validation Package Received by DPA: 9/4/2015

Date Samples Received by DPA: 10/2/2015

Date Analytical Completed by DPA: 1/14/2016

Laboratory Classification: 1. Methods are acceptable for control and regulatory purposes.
2. Methods are acceptable with modifications (as stated in accompanying report).
3. Methods are unacceptable for regulatory purposes.



Date: January 25, 2016

From: Jason D. Rodriguez, Ph.D., Chemist, OPQ/OTR/ DPA
Latevi S. Lawson, Ph.D., ORISE Fellow, OPQ/OTR/DPA
Xiaofei Liu, Ph.D., Chemist, OPQ/OTR/ DPA
Michael E. Hadwiger, Ph.D., Chemist, OPQ/OTR/DPA

To: William Adams, CMC Reviewer, ONDP

Through: Michael Trehy, Ph.D., Lab Chief Branch II, OPQ/OTR/ DPA

Subject: Method Validation for NDA 208551 Triferric

The following methods were evaluated and are acceptable for quality control and regulatory purposes pending address of comments for revision and modification contained in this memo:

1. Determination of (b) (4) in Soluble Ferric Pyrophosphate (SFP) API and Concentrate by UV-Vis Spectroscopy
(Applicant Method: (b) (4) Method Number M11281.00)
2. Identification - Total Iron by Inductively Coupled Plasma – Optical Emission Spectroscopy (ICP-OES) (Applicant Method: MD-91-14)

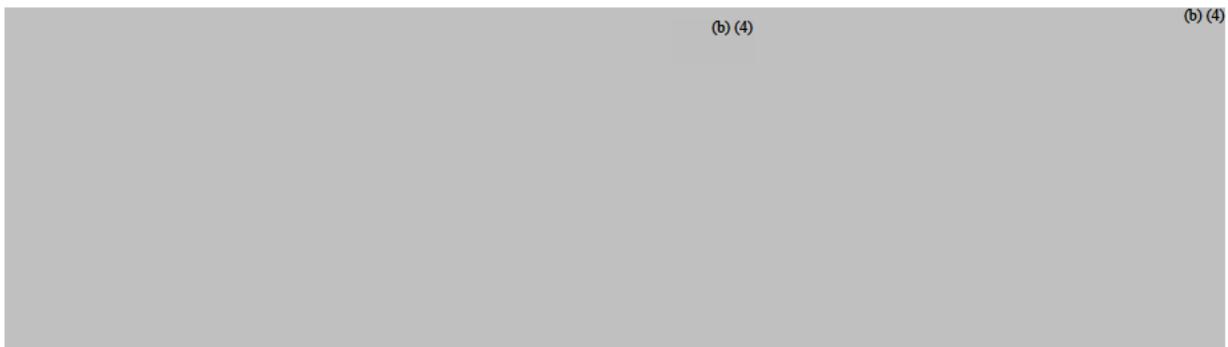
Link to analyst's work sheets and chromatograms:

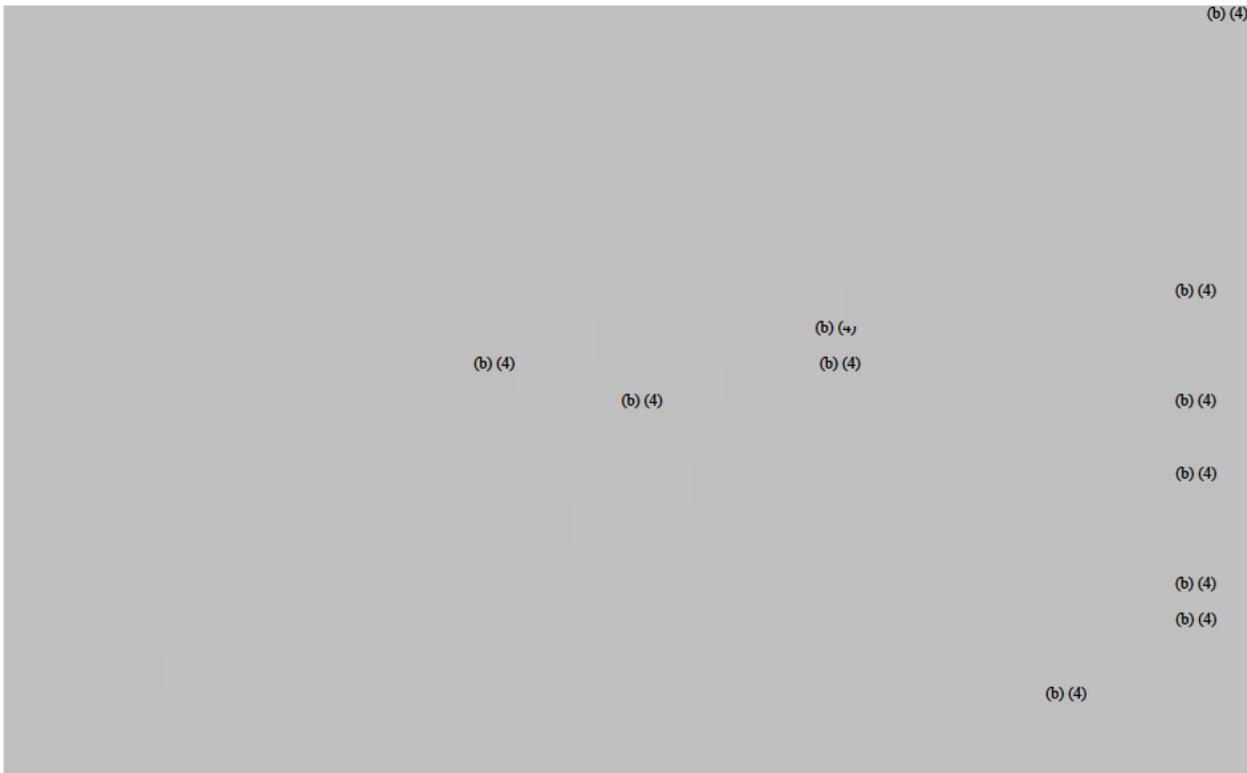
<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f880c5e86e>

Comments:

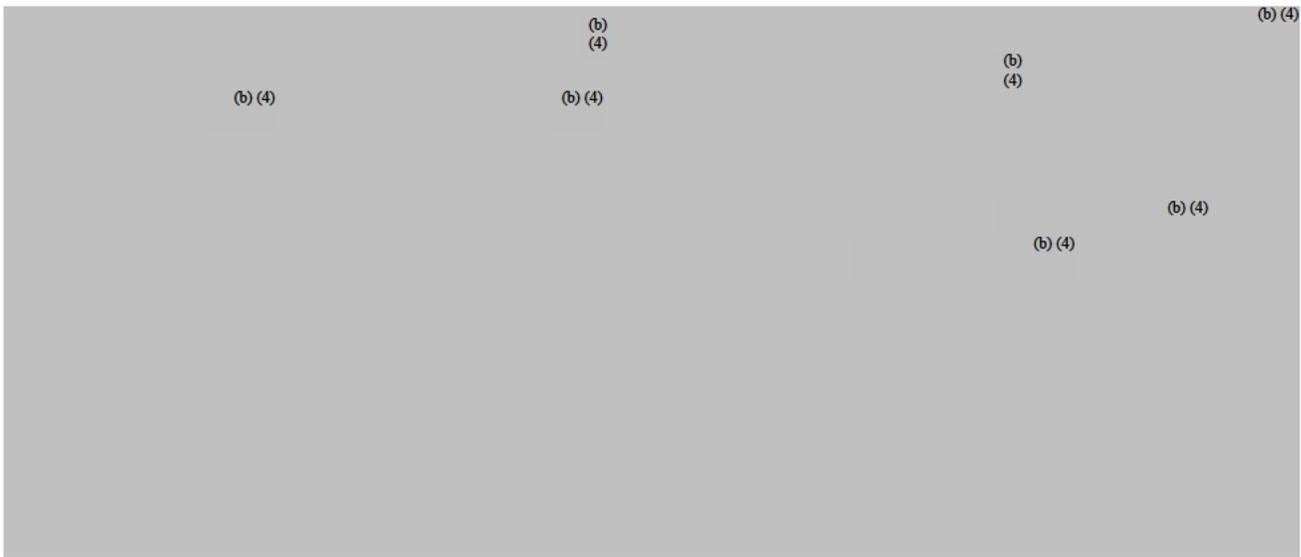
Determination of (b) (4) in Soluble Ferric Pyrophosphate (SFP) API and Concentrate by UV-Vis Spectroscopy
(Applicant Method: (b) (4) Method Number M11281.00)

DPA has the following suggestions regarding the methods:





Identification - Total Iron by Inductively Coupled Plasma – Optical Emission Spectroscopy (ICP-OES) (Applicant Method: MD-91-14)



(b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MICHAEL E HADWIGER
01/26/2016

MICHAEL L TREHY
01/26/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REQUEST FORM

TO: FDA
Division of Pharmaceutical Analysis
Attn: Laura C. Pogue, Ph.D.
645 S. Newstead Avenue
St. Louis MO 63110

FROM: William Adams, CMC Reviewer
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Phone: (301)-796-1652

Through: Olen Stephens, Branch Chief
Phone: (301)-796-3901

and

Rabiya Laiq, Methods Validation Project Manager
Phone: (240)-402-6153:

SUBJECT: Methods Validation Request

Application Number: NDA 208551

Name of Product: TRIFERIC (ferric pyrophosphate citrate) powder for solution, 272 mg iron (III).

Applicant: Rockwell Medical Inc.

Applicant's Contact Person: Raymond Pratt, MD

Address: 30142 S. Wixom Road, Wixom, MI 48393

Telephone: 248 960 9009 Email: rpratt@rockwellmed.com

Date NDA Received by CDER: **6/25/2015**

Submission Classification/Chemical Class: new c

Date of Amendment(s) containing the MVP: **NA**

Special Handling Required:

DATE of Request: **8/28/2015**

DEA Class:

Requested Completion Date: **12/1/2015**

Format of Methods Validation Package (MVP)

User Fee Goal Date: **4/25/2016**

Paper Electronic Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the Methods Validation Requestor and the Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the Methods Validation Requestor and the Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the

laboratory director or by someone designated by the director via DARRTS. The CMC Reviewer, Methods Validation Project Manager, and CMC Lead/Branch Chief should be included as cc: recipients for this document.

All information relative to this application is to be held confidential as required by 21 CFR 314.430.

| | | | | |
|--------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|-------------------------------------|---------------------------------------|--------------------------------|
| MVP Reference # | METHODS VALIDATION REQUEST | | | NDA # 208551 |
| ⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT | | | | |
| ITEM | QUANTITY | CONTROL NO. OR OTHER IDENTIFICATION | | |
| | | | | |
| ⇒ ITEM 2: Contents of Attached Methods Validation Package | | | | Volume/Page Number(s) |
| Statement of Composition of Finished Dosage Form(s) | | | | 3.2.P.1 |
| Specifications/Methods for New Drug Substance(s) | | | | 3.2.S.4.1 |
| Specifications/Methods for Finished Dosage Form(s) | | | | 3.2.P.5.1 |
| Supporting Data for Accuracy, Specificity, etc. | | | | DS: 3.2.S.4.3 DP: 3.2.P.5.3 |
| Applicant's Test Results on NDS and Dosage Forms | | | | |
| Other: | | | | |
| ⇒ ITEM 3: REQUESTED DETERMINATIONS Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate. | | | | |
| Method ID | Method Title | Volume/Page | MV Request Category (see attached) | Comments |
| 505094001 - I | Identification – Ferric Iron by Inductively Coupled Plasma - Optical Emission Spectroscopy | 3.2.S.4.2 | 0 - New dosage form | |
| 505094001 - ICID | Identification – Pyrophosphate by I | 3.2.S.4.2 | 0 - New dosage form | |
| 505094001 - SO4C1, PO4C1, P2O7C1, CITC1 | Assay – Sulfate, Phosphate, Citrate, Pyrophosphate by Ion Chromatography | 3.2.S.4.2 | 0 - New dosage form | |
| 505094001 – NaC1 | Assay – Sodium by Ion Chromatography | 3.2.S.4.2 | 0 - New dosage form | |
| 505094001 – ICPOES | Assay – Iron by Inductively Coupled Plasma - Optical Emission Spectroscopy | 3.2.S.4.2 | 0 - New dosage form | |
| Additional Comments: The methods for testing of the DS and DP are the same | | | | |

Methods Validation Request Criteria

| MV Request Category | Description |
|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 0 | New Molecular Entity (NME) application, New Dosage Form or New Delivery System |
| 1 | Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods) |
| 2 | Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms) |
| 3 | Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay) |
| 4 | Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product) |
| 5 | Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method) |
| 6 | Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation) |
| 7 | Methods that are subject to a “for cause” reason |

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/s/

RABIYA LAIQ
09/04/2015