CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206317Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

Product Quality Microbiology Review

01 DEC 2014

NDA: 206317

Drug Product Name
Proprietary: Triferic™
Non-proprietary: Soluble Ferric Pyrophosphate

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
24 Mar 2014	24 Mar 2014	28 Mar 2014	28 Mar 2014
16 Sep 2014	16 Sep 2014	N/A	N/A
30 Oct 2014	30 Oct 2014	N/A	N/A

Applicant/Sponsor
Name: Rockwell Medical, Inc.
Address: 30142 S. Wixom Road
Wixom, Michigan 48393
Representative: Robert L. Chioini
Telephone: 248-960-9009

Name of Reviewer: Neal J. Sweeney, Ph.D.

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: 505 (b) (1) Original NDA

2. SUBMISSION PROVIDES FOR: Marketing of new drug product

3. MANUFACTURING SITES:

Site 1 (b) (4)
Holopack Verpackungstechnik GmbH (a.k.a. (b) (4)
(b) (4)

(b) (4)

(b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Soluble ferric pyrophosphate concentrate solution (5.44 mg Fe/mL) in 5 mL single use LDPE (b) (4) ampoules for admix with the liquid bicarbonate concentrate used for hemodialysis.

5. METHOD(S) OF STERILIZATION:
(b) (4)

6. PHARMACOLOGICAL CATEGORY: Indicated for treatment of iron loss or iron deficiency to maintain hemoglobin in adult patients with hemodialysis-dependent stage 5 chronic kidney disease (CKD 5HD).

B. SUPPORTING/RELATED DOCUMENTS:
Holopack Site Master File (included in the submission)

C. REMARKS:

A teleconference between the applicant and FDA CMC reviewers was held (August 11, 2014) to discuss the intended use (including admix preparation storage and administration) of the proposed drug product. The applicant subsequently filed an amendment (Sept. 16, 2014) addressing intended product use and administration. Additionally, a Microbiology information request was issued on Sept. 18, 2014, and a corresponding IR response was received by the Agency on Oct. 3, 2014. The Microbiology IR pertained to issues relating to quality microbiology in-process

controls, (b) (4) integrity test acceptance criteria, equipment (b) (4) process validation, and (b) (4)

File name: N206317R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommended for Approval.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The drug product is (b) (4) .

B. Brief Description of Microbiology Deficiencies – Based upon the information provided, no microbiology deficiencies were identified.

C. Contains Potential Precedent Decision(s)- ☐ Yes ☒ No
(If yes, provide a brief description and a reference to the page where the precedent is discussed in depth)

III. Product Quality Microbiology Risk Assessment

A. Initial Product Quality Microbiology Risk Assessment

CQA	Risk Factor	Prob. of Occ. (O)	Modifier for O[3, 4, 5]	Severity of Effect (S)	Detect. (D)	Risk Priority Number[6] (RPN)	Additional Review Emphasis based on Risk (in addition to normal review process)
Ster.	(b) (4)	9	9	5	5	225	(b) (4)
Endo		4	4	4	4	64	

(b) (4)

6 = RPN = O(after modification when applicable)×S×D
RPN <50 = Low Risk; RPN 50-120 = Moderate Risk; RPN >120 = High Risk

Reviewer's Note: Although the drug product is sterile, it is added to a non-sterile dialysis solution for administration via dialysis. Following admixture with the non-sterile bicarbonate

dialysis solution, the resulting solution may be stored up to 24 hours at RT prior to use. As the drug product is added to dialysis solution (rather than direct administration), and the admix storage instructions comply with standard dialysis practice (ANSI/AAMI/ISO 13958 and Centers for Medicare & Medicaid Services guidelines), no sterility or endotoxin modifiers were assigned in the above initial product quality microbiology risk assessment. Additionally the manufacturing process utilizes (b) (4) technology, considered to be more of a (b) (4) rather than an (b) (4) process.

B. Final Risk Assessment -

The (b) (4) manufacturing process, including (b) (4) were validated according to industry standards and comply with current FDA review standards. The manufacturing process includes (b) (4) . Container/closure integrity was adequately validated, and the manufacturing process includes 100% visual inspection and 100% leak testing. Although control of the drug product includes sterility and endotoxin testing, drug product labeling indicates that the drug product is added to (b) (4) bicarbonate dialysis concentrate (and further diluted with the acid concentrate and water for dialysis), and not injected directly into the patient. Therefore, the applicant has mitigated the risks of drug product non-sterility and endotoxin content.

IV. Administrative

A. Reviewer's Signature _____
Neal J. Sweeney, Ph.D.

B. Endorsement Block _____
John W. Metcalfe, Ph.D.

C. CC Block
N/A

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

S DRUG SUBSTANCE

The drug substance, manufactured by (b) (4) is a yellow/green (b) (4) with a (b) (4) acceptance criterion of (b) (4)% (w/w). Microbiological control of the drug substance includes bacterial endotoxin and bioburden release testing, with the following acceptance criteria:

Bacterial Endotoxins test:	(b) (4) EU/mg
Total Aerobic Microbial Count:	(b) (4) CFU/g
Total Combined Molds and Yeasts Count:	CFU/g

ADEQUATE

REVIEWER COMMENT – Microbiological quality acceptance criteria comply with those specified by USP (b) (4) for pharmaceutical use.

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

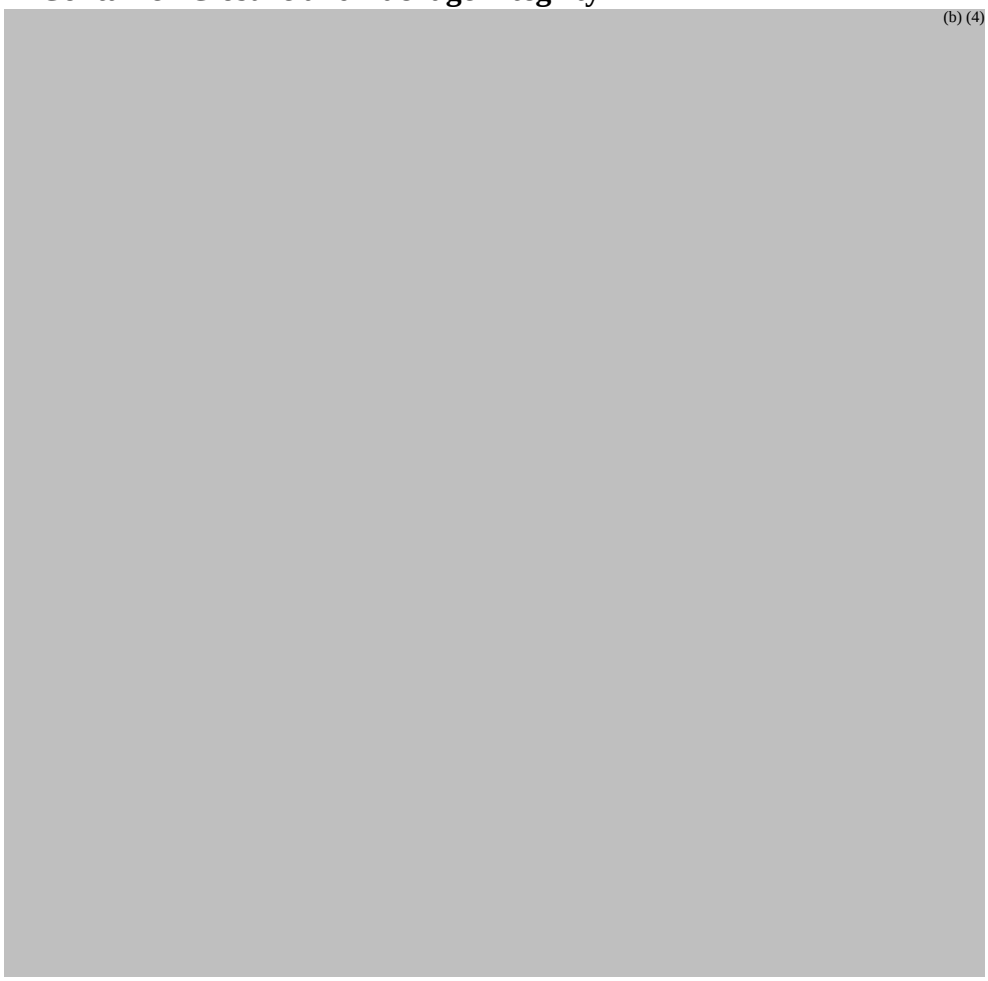
- **Description of drug product –** The drug product Soluble Ferric Pyrophosphate (SFP) Concentrate is a clear, green or greenish-yellow, sterile solution containing 5.44 mg Fe/mL in water (Water for Injection, USP), packaged in 5 mL size (b) (4) low density polyethylene (LDPE) (b) (4) containers (ampoules). At the time of use, the drug product is admixed, (b) (4) with liquid bicarbonate concentrate (b) (4)
- **Drug product composition –**
  Each 5 mL ampoule contains 27.2 mg iron (5.44 mg/mL) in the form of soluble ferric pyrophosphate in 5 mL Water for Injection.
- **Description of container closure system –**
  The primary packaging of SFP (b) (4) is a (b) (4) LDPE ampoule (b) (4) The secondary packaging is a pouch made of an aluminum foil, (b) (4).

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- **Container-Closure and Package integrity -**

(b) (4)



- **Preservative Effectiveness –** N/A The drug product is labeled for single use, and does not contain a preservative.
- **Justification for not having a microbial limit specification for a non-sterile drug product –** N/A The drug product is sterile.

ADEQUATE

REVIEWER COMMENT – Description of drug product and pharmaceutical development information were consistent with the FDA Guidances for Industry: (1) Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, and (2) Q8(R2) Pharmaceutical Development.

P.3 Manufacture

P.3.1 Manufacturers

Drug product manufacture, packaging, release testing and stability testing will all be performed at the following cGMP facility:

Site 1 (b) (4)

Holopack Verpackungstechnik GmbH, (b) (4) Germany

(b) (4)

P.3.3 Description of the Manufacturing Process and Process Controls

(b) (4) **MANUFACTURING PROCESS (DRUG PRODUCT)**

(b) (4)

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

REVIEWER COMMENT – Validation/requalification studies and results were consistent with those delineated in the FDA Guidances for Industry (1) Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, and (2) Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice, as well as common industry practice.

P.5 Control of Drug Product
P.5.1 Specifications
P.5.2 Analytical Procedures

- Endotoxin – USP <85> Bacterial Endotoxins Testing (Limulus Amebocyte Lysate (LAL) gel clot testing (Procedure MB031), is performed (both release and stability) for the drug product. Release and Stability specifications list the acceptance criterion as "(b) (4) EU/mL". (b) (4)

(b) (4)

(b) (4)

- Sterility – Drug product sterility testing (release and stability) is performed according to method MB028 which complies with USP <71>. (b) (4)

(b) (4)

(b) (4)

ADEQUATE

REVIEWER COMMENT – The drug product specification (sterility and bacterial endotoxins testing) and validations comply with USP <1> Injections, <71> Sterility Test, and <85> Bacterial Endotoxins Test, as well as FDA Guidance for Industry: Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.

P.7 Container Closure System (description of container closure system if complicated or unusual requiring a more detailed description than provided in P.1)

P.8 Stability

P.8.1 Stability Summary and Conclusion

MAINTENANCE OF MICROBIOLOGICAL CONTROL AND QUALITY: STABILITY CONSIDERATIONS

P.8.2 Post-Approval Stability Protocol and Stability Commitment

The applicant commits to placing the first three commercial production batches of drug product on long-term stability at 25°C ± 2°C/60% RH ± 5% RH for the proposed (b) (4) month shelf life and for 6 months at 40°C ± 2°C/75% RH ± 5% RH accelerated stability. Thereafter, one production batch per year will be placed on long-term stability. Both sterility and bacterial endotoxins testing are performed at the 0, 12, 24, and 36 month long-term stability test stations, and at the 0 and 6 month accelerated stability test stations.

P.8.3 Stability Data

Stability data for Triferic™ batches LP174, ME020, ME023, and NE332 demonstrated that samples stored under accelerated (0 and 6 months) and long term conditions (0, 12, 24, and 30 months) met the proposed acceptance criteria for bacterial endotoxin and sterility testing.

ADEQUATE

REVIEWER COMMENT – The submitted stability protocol, commitment and data complies with Guidances for Industry: (1) Q1A(R2) Stability Testing of New Drug Substances and Products, and (2) Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

None of the components used in manufacture of the drug product are of human or animal origin.

R REGIONAL INFORMATION

R.1 Executed Batch Record

Executed batch records for Triferic™ (soluble ferric pryophosphate) exhibit batches LP174, ME020, ME023, and NE332 were provided. Corresponding sterility test endotoxin test results for each batch met established acceptance criteria.

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)
MODULE 1

A. PACKAGE INSERT

The package insert specifies that the contents of the Triferic drug product ampoule are added (b) (4) to 2.5 gallons of bicarbonate dialysis concentrate, (b) (4) . The package insert also specifies that following addition of Triferic to the bicarbonate concentrate, the resulting bicarbonate concentrate mixture must be used within 24 hours after preparation. The storage instructions comply with the ANSI/AAMI/ISO 13958 which states that bicarbonate concentrate should be used within 24 hours after opening. Additionally, standard dialysis practice and CMS (Centers for Medicare & Medicaid Services) require bioburden and endotoxin testing of the dialysate solution used during each dialysis shift. ANSI/AAMI/ISO 11663 action levels for dialysate bioburden and endotoxin are 50 CFU/mL and 0.25 EU/ml, respectively

ADEQUATE

REVIEWER COMMENT – Use and storage of the diluted drug product comply with ANSI/AAMI/ISO 13958, as well as standard dialysis practice established by CMS (Centers for Medicare & Medicaid Services).

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

(none)

Reviewer's Signature Neal J. Sweeney -A

Digita ly signed by Neal J Sweeney A
DN c=US o=U S Government ou=HHS ou=FDA ou=People 0 9 2342 19200300 100 1 1=1300109587 cn=Neal J Sweeney A
Date 2014 12 03 15 48 27 05 00'

Neal J. Sweeney, Ph.D.

Endorsement Block John W. Metcalfe -A

Digitally signed by John W Metcalfe A
DN: c=US, o=U S Government, ou=HHS, ou=FDA, ou=People, 0 9 2342 19200300 100 1 1=1300198103, cn=John W Metcalfe A
Date: 2014 12 03 16:14:17 05'00'

John W. Metcalfe, Ph.D.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 206317 **Applicant:** Rockwell Medical, Inc. **Letter Date:** 3/24/14

Drug Name: Triferic (Soluble Ferric Pyrophosphate) **NDA Type:** 505(b)(1) Standard **Stamp Date:** 3/24/14

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		eCTD
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		(b) (4) (b) (4)
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		(b) (4)
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	X		Holopack sterilization process validation reports
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	X		3.2.P.2. C/C integrity (b) (4) , No preservative requirement (single use for dialysis)
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		3.2.P.5.1. (release and stability) sterility and endotoxin), 3.2.P.5.6.6 justification of endotoxin spec
7	Has the applicant submitted the results of analytical method verification studies?	X		3.2.P.5.3 (sterility and endotoxin testing)
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	N/A	N/A	No product quality microbiology studies or information were requested during the Sept. 9, 2013 PreNDA meeting.
9	If sterile, are extended post-constitution and/or post-dilution hold times in the draft labeling supported by microbiological data?	N/A	N/A	No labeling instructions for post-constitution/storage. Single use, administration via hemodialysis dialysate
10	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: (none)

22 April 2014

Neal J. Sweeney, Ph.D., Reviewing Microbiologist Date

Bryan S. Riley, Ph.D., Acting Team Leader Date

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

/s/

NEAL J SWEENEY
04/23/2014

BRYAN S RILEY
04/23/2014
I concur.