CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206317Orig1s000

CHEMISTRY REVIEW(S)

NDA 206317

Triferic® (ferric pyrophosphate citrate) solution
27.2 mg Fe(III)/5 mL

Rockwell Medical, Inc.

William M. Adams
Review Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment

For the Division of Hematology Products
Office of Hematology and Oncology Products

Table of Contents

CMC Review Data Sheet

1. NDA 206317

2. REVIEW #2

3. REVIEW DATE: 20 Jan 2015

4. REVIEWER: William Adams

5. PREVIOUS DOCUMENTS:

S-000	New NDA	03/24/14
S-001	Trade Name	04/03/14
S-008	Updated Package Insert	06/23/14
S-014	Updated Carton Labels	08/04/14
	Tcon re CMC issues	08/11/14
S-021	Quality Microbiology	09/16/14
	IR – CMC comments	09/18/14
S-023	Quality CMC response to 09/18/14 IR letter	10/03/14
	IR; pouch & carton comments	10/07/14
S-033	Updated Labels	10/24/14

6. SUBMISSION(S) BEING REVIEWED:

	IR; dose preparation question	10/23/14
S-033	Updated pouch & cartons labels	10/24/14
S-036	In-Use stability study	10/30/14
	IR: package insert comments	12/12/14
	IR; pouch and carton comments	12/18/14
S-041	In-Use stability study	12/23/14
S-043	Updated carton & pouch labels	12/29/14
S-044	Updated package insert	12/29/14
	Email with updated ampule labels (not in Daarts)	01/12/15
S-046	Accept USAN name	01/16/15
	Email updated labels & labeling	01/19/15

7. NAME & ADDRESS OF APPLICANT:

Name: Rockwell Medical, Inc.
Address: 30142 Wixom Road
Representative: Wixom, MI 48393
Telephone: 248-960-9009

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Triferic

CMC Review Data Sheet

b) Non-Proprietary Name (USAN): Ferric Pyrophosphate Citrate
c) Code Name/# (ONDQA only): H61
d) Chem. Type/Submission Priority (ONDQA only):

- **Chem. Type:** 1
- **Submission Priority:** Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

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

11. DOSAGE FORM: Solution Concentrate for Hemodialysis

12. STRENGTH/POTENCY: 27.2 mg Fe (III)/5 mL (5.44 mg Fe(III)/mL)

13. ROUTE OF ADMINISTRATION: Hemodialysis

14. Rx/OTC DISPENSED: __√__ **Rx** ___ **OTC**

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed
__√__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: See CMC Review 01

17. RELATED/SUPPORTING DOCUMENTS: See CMC Review 01

18. CONSULTS/CMC-RELATED REVIEWS: See CMC Review 01

The CMC Review for NDA 206317

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for APPROVAL from the chemistry, manufacturing and control (CMC) perspective.

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

None

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

See CMC Review 01 for Quality information. Final negotiation of the package insert is on-going.

B. Description of How the Drug Product is Intended to be Used

Triferic® is intended to be added to the bicarbonate concentrate component of hemodialysate solution. The final concentration of iron (III) in hemodialysate is 2 µM (110 µg/L).

C. Basis for Approvability or Not-Approval Recommendation

The application is recommended for APPROVAL from the CMC perspective in that adequate and acceptable information has been provided to establish the quality and stability of the proposed drug substance and drug product.

III. Administrative

A. Reviewer's Signature:

Digitally signed by William M. Adams -A
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 -A
Date: 2015.01.22 13:29:05 -05'00'

William M. Adams
CMC Reviewer/Branch II/DNDQA I/ONDQA

B. Endorsement Block:

Ali H. Al- Hakim -A

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300093815, cn=Ali H. Al- Hakim -A
Date: 2015.01.22 14:05:41 -05'00'

Ali al Hakim, Ph.D.
Chief/Branch II/DNDQA I/ONDQA

C. CC Block:

DHP/RPM/A.Chi
DNDQA I/PMQ/A.Teicher
DNDQA I/CMC Lead/J.Brown

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- In section 12.1, delete the statement [redacted] (b) (4) in line 1; inappropriate statement for this section.
- DMEPA noted that, for consistency, product strength should be presented as "27.2 mg iron (III)/5 mL (5.44 mg iron (III)/mL)", throughout the labels and labeling; revise section 16.1 to include the latte part of the strength statement. Carton and Pouch labels already use this strength statement.

FOLLOW-UP

01/16/15 Amendment S-046; applicant accepted the USAN accepted drug established name.
01/16/15 FDA Email response with comments on draft labels and labelins
01/19/15 Applicant Email with revised ampule, pouch & carton labels; and package insert. The applicant accepted all changes in the ampule, pouch, and carton labels; and the USAN drug established name. Applicant proposed revisions and comments on the FDA proposed PI were provided.

Evaluation

Ampule, pouch and cartons are Acceptable for CMC.

CMC discussion continues on PI section 2.1. All other applicant proposed revision to the PI were non-CMC related.

ENVIRONMENTAL ASSESSMENT

Evaluation

Acceptable in CMC Review 01

3.2.III. LIST OF DEFICIENCIES TO BE COMMUNICATED

None

NDA 206317

Triferic® (ferric pyrophosphate citrate) solution 27.2 mg Fe(III)/5 mL

Rockwell Medical, Inc.

William M. Adams
Review Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment

For the Division of Hematology Products
Office of Hematology and Oncology Products

Table of Contents

CMC Review Data Sheet

1. NDA 206,317

2. REVIEW #1

3. REVIEW DATE: 17 Dec 2014

4. REVIEWER: William Adams

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

S-000	New NDA	03/24/14
S-001	Trade Name	04/03/14
S-008	Updated Package Insert	06/23/14
S-014	Updated Carton Labels	08/04/14
	Tcon re CMC issues	08/11/14
S-021	Quality Microbiology	09/16/14
S-023	Quality CMC response to 09/18/14 IR letter	10/03/14
S-033	Updated Labels	10/24/14

7. NAME & ADDRESS OF APPLICANT:

Name: Rockwell Medical, Inc.
Address: 30142 Wixom Road
Representative: Wixom. MI 48393
Telephone: 248-960-9009

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Triferic
b) Non-Proprietary Name (USAN): Soluble Ferric Pyrophosphate (proposed)
c) Code Name/# (ONDQA only): H61
d) Chem. Type/Submission Priority (ONDQA only):

- **Chem. Type:** 1
- **Submission Priority:** Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

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

11. DOSAGE FORM: Solution Concentrate for Hemodialysis

12. STRENGTH/POTENCY: 5.44 mg Fe (III)/mL

13. ROUTE OF ADMINISTRATION: Hemodialysis

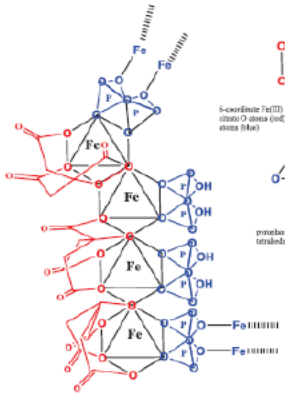
14. Rx/OTC DISPENSED: **__√__Rx** **___OTC**

15. <u>SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):</u>

_____SPOTS product – Form Completed
__√__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Molecular Formula $(Fe^{+3})_4(C_6H_5O_7^{-4})_3(P_2O_7^{-4})_3$
Molecular Weight 1301.4 amu
Molecular Structure



B

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted

6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
IND 051290			active		

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	REVIEWER	STATUS
EES	GMP status of CMC Facilities		V.Dholakia	Acceptable
ClinPharm/ Biopharm	Bioavailability		O.Okusanya/ B.Zolnik	Acceptable
Microbiology	Sterility Assurance		N. Sweeney	Acceptable

The CMC Review for NDA 206317

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for APPROVAL from the chemistry, manufacturing and control (CMC) perspective.

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

None

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

DRUG SUBSTANCE

The established name for drug substance is awaiting a decision by the USAN Committee.

Ferric Pyrophosphate Citrate is composed of octahedral coordination complexed formed from ferric ion surrounded by pyrophosphate and citrate ligands. The active moiety is stated to be four complexes in sequence and sequences complexes share pyrophosphate and citrate ligands. The active moiety and bulk material has been characterized by mass spectrometry, x-ray analysis, elemental analysis and ion content. Bulk drug material is yellow-green, (b) (4) and very soluble in water.

Bulk drug is manufactured by a (b) (4) The synthesis process, process controls and material specifications are adequate for the intended purpose and described in sufficient detail. Packaging for the storage and shipment of bulk material provides (b) (4).

Each site proposed for manufacture and testing has been found to meet GMP standards.

The release specification (tests, analytical methods and acceptance criteria) have been described is sufficient detail and the methods have been validated for their intended purpose. The proposed acceptance criteria have been accepted. Appropriate reference standards have been established. A specification for (b) (4) is to be established upon after validation of the manufacturing and the analytical method. The criterion for residual solvent will be re-evaluated upon completion of process validation.

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

DRUG PRODUCT

Executive Summary Section

Triferic® (ferric pyrophosphate citrate) Concentrated Solution for Administration by Hemodialysis is a solution of drug substance dissolved in water with a strength of 27.2 mg Fe(III)/5mL. The commercial presentation is a set of five ampules filled with 5 mL of solution which are stored in an opaque, laminate pouch within a cardboard carton.

The product is intended to be admixed into commercially available bicarbonate solution (b) (4)

Product manufacture is by a (b) (4) (b) (4) The manufacturing process, process controls and material specifications are adequate for the intended purpose and described in sufficient detail.

Each site proposed for manufacture and testing has been found to meet GMP standards.

The release specification (tests, analytical methods and acceptance criteria) have been described is sufficient detail and the methods have been validated for their intended purpose. The proposed acceptance criteria have been accepted. Appropriate reference standards have been established. A specification for (b) (4) is to be established upon after validation of the manufacturing and the analytical method.

The packaging components are the ampule, the pouch and a cardboard carton. Ampules, constructed from low density polyethylene (b) (4), form a (b) (4) container for the solution. The pouch, formed from a (b) (4)-aluminum laminate film, provides light protection for the ampules. Materials of composition, dimensions and acceptance specification for the ampule and pouch materials are described in sufficient detail. Extractables and leachables studies are provided to qualify the safety of the ampoule and pouch materials.

In-use stability studies establish that the product-bicarbonate and hemodialysate solutions are stable for up to 24 hours at room temperature.

The primary stability study data and information is sufficient to establish that drug product is stable for 24 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) when the ampules are maintained within their pouch.

The proposed vial, pouch and carton labels, and the proposed package insert are currently being negotiated.

B. Description of How the Drug Product is Intended to be Used

Triferic® is intended to be added to the bicarbonate concentrate component of hemodialysate solution. The final concentration of iron (III) in hemodialysate is 2 µM (110 µg/L).

C. Basis for Approvability or Not-Approval Recommendation

The application is recommended for APPROVAL from the CMC perspective in that adequate and acceptable information has been provided to establish the quality and stability of the proposed drug substance and drug product.

III. Administrative

Executive Summary Section

A. Reviewer's Signature:

Digitally signed by William M. Adams -A
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 -A
Date: 2014.12.17 11:07:55 -05'00'

William M. Adams
CMC Reviewer/Branch II/DNDQA I/ONDQA

B. Endorsement Block:

Ali H. Al- Hakim -S

Digitally signed by Ali H. Al- Hakim -S
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Date: 2014.12.17 15:07:57 -05'00'

Ali al Hakim, Ph.D.
Chief/Branch II/DNDQA I/ONDQA

C. CC Block:

DHP/RPM/A.Chi
DNDQA I/PMQ/A.Teicher
DNDQA I/CMC Lead/J.Brown

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Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: 06-Aug-2014

From: Janice Brown, M.S.
CMC Lead
DNDQA I/ONDQA

Through: Ali Al-Hakim, Ph.D.
Chief, Branch II
New Drug Quality Assessment Division I1
ONDQA

To: NDA 206317
Ferric pyrophosphate solution

Subject: Risk Assessment

As per a new policy, each NDA with GRMP dates on or after August 1, 2014 will include a risk assessment in the Executive summary. This will be based on an initial risk assessment that would be captured in all IQAs written for NDAs received on or after June 1, 2014. It was decided that the CMC Lead would perform a retrospective risk assessment for those NDAs received prior to June 1, 2014 that had GRMP dates after August 1, 2014.

The following IQA template was provided:

ONDQA Risk Assessment Template for Initial Quality Assessments of Original NDAs

Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment

In an email dated 30-May-2014, Dr. Ramesh Sood provided follow-up guidance on how to fill out the required IQA template that is used to populate the NDA template. The guidance provided templates for the most common dosage forms.

This memo captures both the table that would normally be in the IQA and populates the first three columns of the NDA template that will be filled in by the primary CMC reviewer.

IQA RISK ASSESSMENT

Product attribute/ CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment	Risk
Sterility	• Formulation • Container closure • Process parameters • Scale/equipment • Site	4	5	5	100		H
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipment • Site	2	4	4	32		M
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	3 (Mod stable drug)	2	5	30	There is no DP test for impurities so D was assigned 5 and O as a moderately stable drug which is defined as: No single impurity (b) (4) %; Total impurities (b) (4) %	M
Uniformity of Dose (Fill Volume/ Deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	4	4 (HRD)	5	80	Applicant does <u>not</u> perform density determination prior to filling and does not meet the USP <1151> excess volume recommendation ((b) (4) mL). (The target fill for this product is ≤ (b) (4) to (b) (4)	H
pH- (High)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	3	4	1	12		L
pH- (Low)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	2	2	1	4		L
Leachable extractables	• Formulation • Container closure • Process parameters • Scale/equipment • Site	2	4	3	24		L
Appearance (Color/turbidity)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	3	3	1	9		L

The evaluation from the IQA table was transferred to the following NDA table that can be used by the primary reviewer as a part of the NDA review.

NDA RISK ASSESSMENT TABLE

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking**	**Risk Mitigation approach**	**Risk Evaluation**	**Lifecycle Considerations / Comments**
Sterility	• Formulation • Container closure • Process parameters • Scale/equipment • Site	H			
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipment • Site	M			
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	M			
Uniformity of Dose (Fill Volume/ Deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	H			
pH- (High)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L			
pH- (Low)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L			
Leachable extractables	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L			
Appearance (Color/turbidity)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L			

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

/s/

JANICE T BROWN
08/18/2014

ALI H AL HAKIM
08/18/2014

Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre-Marketing Applications (Original)

I. Review Cover Sheet

1. OMPQ Reviewer: **Vipul Dholakia**

2. NDA/BLA Number: **NDA 206-317**
Submission Date: **03/24/2014**
21st C. Review Goal Date: **11/25/2014**
PDUFA Goal Date: **01/24/2015**

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	**Triferic**
Established or Non-Proprietary Name (USAN) and strength:	**Soluble Ferric Pyrophosphate**
Dosage Form:	**Sterile Concentrate Solution**

4. SUBMISSION PROPERTIES:

Review Priority :	**Standard**
Applicant Name:	**Rockwell Medical, Inc.**
Responsible Organization (OND Division):	**DHP**

II. Application Detail

INDICATION: Treatment of iron loss or iron deficiency to maintain hemoglobin in adult patients with hemodialysis-dependent stage 5 chronic kidney disease(CKD 5HD)

1. ROUTE OF ADMINISTRATION: Hemodialysis

2. STRENGTH/POTENCY: 5.44 mg Fe/mL

3. Rx/OTC DISPENSED: ☒Rx ☐OTC

4. ELECTRONIC SUBMISSION (yes/no)? Yes

5. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V		X		
2.	Breakthrough Therapy Designation		X		
3.	Orphan Drug Designation		X		
4.	Unapproved New Drug		X		
5.	Medically Necessary Determination		X		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		X		
7.	Rolling Submission		X		
8.	Drug/device combination product with consult		X		
9.	Complex manufacturing		X		
10	Other (e.g., expedited for an unlisted reason)		X		

III. FILING CHECKLIST

The following parameters are necessary in order to initiate a full review (i.e., the application is complete enough to start review but may have deficiencies). On **initial** review of the NDA application:

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	**Yes**	**No**	**Comment**
11.	Is a single comprehensive list of all involved facilities available in one location in the application?	X		
12.	Is all site information complete (e.g., contact information, responsibilities, address)?	X		
13.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	X		
14.	Do all sites indicate they are ready to be inspected (on 356h)?	X		
15.	Additional notes (non-filing issue) 1. Are all sites registered or have FEI #? 2. Do comments in EES indicate a request to participate on inspection(s)? 3. Is this first application by the applicant?	X	 X X	

*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQ. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
16.	Have any Comparability Protocols been requested?		X	

IMA CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
17.	Does this application fit one of the EES Product Specific Categories?	X		
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?	X		
19.	**From a CGMP/facilities perspective, is the application fileable?** If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	X		

IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements?			
Nanotechnology	RTRT Proposal	PAT	Drug/Device Combo
☐	☐	☐	☐
PET	Design Space	Continuous Mfg	Naturally derived API
☐	☐	☐	☐
Other (explain):	**None**		

Manufacturing Highlights

1. Drug Substance

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	Soluble Ferric Pyrophosphate (SFP) is manufactured (b) (4)

2. Drug Product

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	The manufacturing process for SFP Concentrate (b) (4)

3. Facility-Related Risks or Complexities (e.g., number of foreign sites, large number of sites involved, etc.)

Drug Substance: Soluble Ferric Pyrophosphate is manufactured, and release and stability testing, bulk packaging and release is performed by (b) (4) . Release, and stability testing is also performed by (b) (4) .

V. Overall Conclusions and Recommendations

Is the application filable? Yes **yes**
At this time, is a KTM warranted for any PAI? NO
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? NO
Comments for 74 Day Letter
1.
2.
3.

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REVIEW AND APPROVAL

(DARRTS)

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

/s/

VIPULCHANDRA N DHOLAKIA
05/23/2014

MAHESH R RAMANADHAM
05/23/2014

ONDQA CMC and Biopharmaceutics Filing Review and Initial Quality Assessment
NDA 206317 TRIFERIC® (ferric pyrophosphate) Solution
Rockwell Medical, Inc.

IQA and Filing Review Cover Sheet

1. **NEW DRUG APPLICATION NUMBER:** 206317
2. **DATES AND GOALS:**

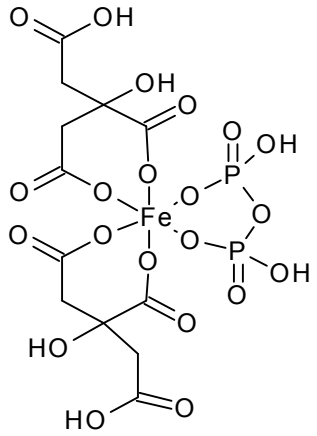
Letter Date: 24-Mar-2014	Received date: 24-Mar-2014
Filing: 05/23/2014 74 Day Filing Issues: 06/06/2014 Proprietary Name Review: 07/02/2014 Mid-Cycle: 24-Aug-2014	Primary Reviews Due: 20-Dec-2014 PDUFA Goal Date -Priority: 01/24/2015

3. **PRODUCT PROPERTIES:**

Trade or Proprietary Name:	Triferic
Established or Non-Proprietary Name (USAN):	Soluble Ferric Pyrophosphate
Dosage Form:	Solution
Route of Administration	Hemodialysis
Strength/Potency	5.44 mg Fe/mL
Rx/OTC Dispensed:	Rx

4. **INDICATION:** Treatment of iron loss or iron deficiency to maintain hemoglobin in adult patients with hemodialysis-dependent stage 5 chronic kidney disease (CKD 5HD)

5. **DRUG SUBSTANCE STRUCTURAL FORMULA:** The co-ordination structure of the iron (III) is presented below:



Molecular formula: $Fe_3(C_6H_5O_7)_2(P_2O_7)_2$
Relative molecular weight: approximately (b) (4) Da

6. NAME OF APPLICANT (as indicated on Form 356h): Rockwell Medical, Inc.

7. SUBMISSION PROPERTIES:

Review Priority:	Standard
Submission Classification (Chemical Classification Code):	Type 5
Application Type:	505(b)(1)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	DHP

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clinical Pharmacology		X	
Establishment Evaluation Request (EER)	X		Entered on 14-Apr-2014
Pharmacology/Toxicology			Determined by primary reviewer
Methods Validation		X	This product is not an NME
Environmental Assessment	X		A claim of categorical exclusion from the requirement to submit an Environmental Assessment (EA) was requested
CDRH	X		Advisory function only since this product will be used in a dialysis machine
Other			N.A.

9. QUALITY REVIEW TEAM:

Discipline	Reviewer
CMC	William (Mike) Adams, B.S.
Biopharmaceutics	Banu Zolnik, Ph.D.
Microbiology	Neal Sweeney, Ph.D.
Facilities	Vipul Dholakia, Ph.D.

ONDQA CMC and Biopharmaceutics Filing Review and Initial Quality Assessment
NDA 206317 TRIFERIC® (ferric pyrophosphate) Solution
Rockwell Medical, Inc.

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? Yes
CMC Filing Issues: None

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? No
CMC Comments for 74-Day Letter: Yes, see below. In order for the Agency to take an action on your application, you will need an established name for the drug product. The established name contains a non-proprietary name for the drug substance and the term "solution" where the dosage form is typically displayed. An official non-proprietary name is either a United States Adopted Name (USAN) or the title of a USP monograph. There is no USAN or USP monograph for ferric pyrophosphate. We note that there is a Food Chemical Codex (FCC) monograph for ferric pyrophosphate. We suggest you submit an application to the USAN council requesting adoption of a USAN for your drug substance.

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? Yes
Biopharmaceutics Filing Issues: None

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? No
Biopharmaceutics Comments for 74-Day Letter: None

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective? Yes
Microbiology Filing Issues: See Microbiology Filing Review for details and for any potential Microbiology review issues.

ONDQA CMC and Biopharmaceutics Filing Review and Initial Quality Assessment
NDA 206317 TRIFERIC® (ferric pyrophosphate) Solution
Rockwell Medical, Inc.

Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
No	No	No	

CMC Summary of Critical Issues and Complexities

1. The drug product name was forwarded to Yana Mille who will discuss with the USP nomenclature group. The applicant proposed the following name:

   TRIFERIC® (soluble ferric pyrophosphate) Concentrate Solution

   After discussion with Yana Mille, the USP Nomenclature, Safety and Labeling Expert Committee discussed the nomenclature for this product. Their decision is that the nonproprietary name should be created using the following format: [Drug] Solution. Therefore, the name of this product is:

   TRIFERIC® (ferric pyrophosphate) Solution

2. After discussion with David Lewis regarding the established name, the following deficiency will be communicated in the 74-day letter:

   In order for the Agency to take an action on your application, you will need an established name for the drug product. The established name contains a non-proprietary name for the drug substance and the term "solution" where the dosage form is typically displayed. An official non-proprietary name is either a United States Adopted Name (USAN) or the title of a USP monograph. There is no USAN or USP monograph for ferric pyrophosphate. We note that there is a Food Chemical Codex (FCC) monograph for ferric pyrophosphate. We suggest you submit an application to the USAN council requesting adoption of a USAN for your drug substance.

3. A CDRH consult specializing in dialysis machines was requested in the event the reviewer needs to discuss issues related to SFP admix and the administration during the dialysis procedure. The admix studies should also be jointly reviewed by both ONDQA, OPS micro and CDRH. CDRH should have the lead on the adequacy of these studies.

4. Drug Substance

   a. The applicant provided virtually no physical and chemical information for their product. (b) (4) the pH solubility profile would be very

useful. The applicant indicated that data was not available for the melting point range, pKa, pH solubility profile, particle size, partition coefficient, and hygroscopicity. This information is relatively easy to obtain and should be requested.

b. The drug substance specification does not include a test for (b) (4) which is an impurity in other iron products.

c. (b) (4) exceed the recommendations in USP <232> for drug substance and excipients. Rockwell has provided a justification explaining that the limits for heavy metal contaminants in SFP drug substance will not exceed (b) (4)% of the AAMI, ISO, and EP water limits. Since the USP does not have a monograph for this product, USP <232> would not apply the drug substance or drug product. Consider requesting testing for elemental impurities in the drug product to ensure levels comply with Q3D or provide a justification why testing would not be needed.

d. Stability results for drug substance batches 0804536, 0804537, and 0804538 failed (b) (4) content at (b) (4) months when stored under long term conditions. These batches also failed (b) (4) content at (b) (4) months under accelerated conditions. As a result of these failures, (b) (4) Batch 1004939 was packaged with (b) (4) met the proposed limits under long term and accelerated conditions.

Surprisingly, the applicant requested a retest date of (b) (4) months. According to Q1E if a significant change occurs at the intermediate condition, the proposed retest period or shelf life should not exceed the period covered by long-term data. Since the results at (b) (4) months were at the (b) (4) content limit of NMT (b) (4)% under long term conditions and failed the same attribute at (b) (4) months under accelerated conditions, a (b) (4) month shelf life is certainly reasonable.

e. A photostability study shows that the drug substance is (b) (4).

Drug Product

5. There are separate drug product release and stability specifications that should be combined into a single drug product specification. According to ICH Q6A, there are universal tests that are considered to be applicable to all new drug products. These tests include appearance, identification, assay, and impurity. Note that the applicant does not perform impurity (elemental impurities) monitoring or content uniformity. Consider requesting this information or a justification why it is not performed.

6. For other iron products, (b) (4) is an impurity that is monitored and controlled. Consider requesting an addition test for (b) (4) or a justification why testing is not routinely performed. Also as mentioned in 3c above, consider requesting testing for elemental impurities in the drug product to ensure levels comply with Q3D.

7. The primary packaging of SFP Concentrate is a [redacted] ampoule made from a low density polyethylene (LDPE). The applicant performed an extraction profile and identified numerous extractables. The extractable report did not include a toxicological evaluation. Recommend producing a table listing all the extractables along with the concentration [redacted] and forward this information to the nonclinical reviewer for their evaluation. Alternatively, an IR can be sent to the applicant requesting this information.

8. Stability results for batches 0804536, 0804537, and 0804538 failed [redacted] content at [redacted] months when stored under long term conditions. These batches also failed [redacted] content under accelerated conditions at [redacted] months. Results for [redacted] were at or near the proposed limit of [redacted]% w/w. As a result of these failures, an aluminum pouch was added as a secondary package. Batch 1004939 was packaged with the aluminum pouch met the proposed limits under long term and accelerated conditions.

   The applicant requested a retest date of [redacted] months. According to Q1E if a significant change occurs at the intermediate condition, the proposed retest period or shelf life should not exceed the period covered by long-term data. In addition, a retest period or shelf life shorter than the period covered by long-term data could also be considered.

   Since the results at [redacted] months were at the [redacted] content limit of NMT [redacted]% under long term conditions and failed the same attribute a [redacted] months under accelerated conditions, a [redacted] month shelf life is certainly reasonable.

9. A photostability study was carried out according to ICH Q1B that shows the SFP drug product is light sensitive. Section 16.2 of the proposed labeling states that the product should be stored in an aluminum pouch.

10. The applicant performed an in-use study was to determine the stability of SFP in bicarbonate concentrate under ambient conditions over a twelve week period. [redacted] Samples were tested at initial, 1 week, 3 weeks, 6 weeks, 9 weeks and 12 weeks after preparation.

    [redacted]
    A similar study was performed on the compatibility of SFP with dialysate and dialyzers.

    Consider requesting a justification for determining acceptable results for both admix studies. [redacted] If it does not represent actual use the validity of these studies are questionable.

Initial Quality-Biopharmaceutics Assessment

Biopharmaceutics Synopsis, Critical Issues or Complexities

Submission:
This 505(b) (1) Application is summited for Triferic™ (soluble Ferric Pyrophosphate or SFP) for the chronic treatment of iron loss, maintenance of hemoglobin and reduction of erythropoiesis-stimulating agents (ESAs) use in adults who are hemodialysis-dependent due to chronic kidney disease.

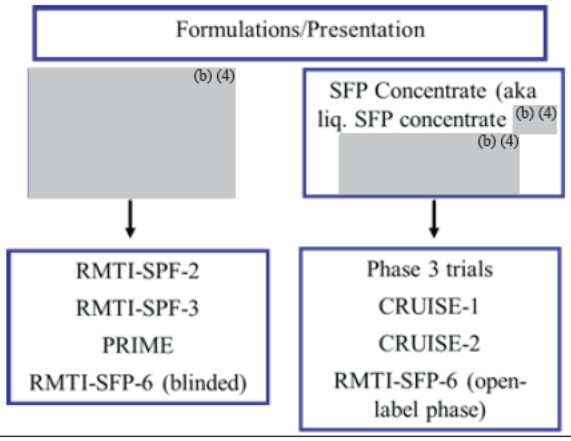
Introduction:
Triferic™ has been developed as a maintenance iron replacement product for patients with chronic kidney disease receiving maintenance hemodialysis (CKD-HD). Triferic is added to the dialysate and delivered with each dialysis treatment. Once Triferic is in the dialysate, it crosses the dialyzer membrane and enters the blood, providing a measured, continues transfer of iron to the patient.

The Applicant conducted the following studies SFP-1, -2, -3, NIH-FP-01 (aka PRIME), SFP-RC (aka CRUISE 1, Stage2), SFP-4-OL (CRUISE 1, Stage 3), SFP-5-RC (CRUISE 2, Stage 2), SFP-5-OL (CRUISE 2, Stage 3), SFP-6-RC, SFP-6-OL, SFP-8 in CKD-HD subjects and SFP 9 study in health volunteers in support of the approval of the proposed drug product.

Product Description:
Soluble Ferric Phyrophosphate (SFP) 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 (b) (4) ampoules. At the time of use, the drug product is admixed (b) (4) with liquid bicarbonate concentrate (b) (4)

The Applicant used two formulations of the soluble ferric pyrophosphate in the clinical development program.

Schematic overview of Triferic Clinical Development



Reviewer's Comments:
The Applicant states that [redacted] ***For SFP concentrate,*** *the Applicant states that this formulation/presentation was chosen to minimize the effect of variable bicarbonate preparation procedures. For this formulation/presentation, drug product is admixed* [redacted] *with liquid bicarbonate concentrate* [redacted]

[redacted]

The Applicant's statement about [redacted] ***the two formulations/presentations*** [redacted] ***SFP concentrate will be evaluated by the CMC Reviewer.***

Composition of the SFP Concentrate Drug Product

Table 2.3.P.1-1. Composition of the SFP Concentrate Drug Product

Ingredients	Function	Quality Standard	Unit (5 mL) Composition Strength (label claim): 5.44 mg Fe/mL Quantity	Percent
Drug Substance				
Soluble Ferric Pyrophosphate (SFP)	Active Ingredient	Reference Standard[a]	27.2 mg Fe[b] (w/w)	0.544% (w/w)
Excipients				
Water for Injection	[redacted]	USP/Ph.Eur.	q.s. to volume 5 mL	- 100.00% (w/w)
Total				

[a] Refer to Module 2.3.S.5.
[b] Iron (Fe) content of SFP is 7.5% - 9.0% w/w. [redacted]

Review Objectives:
The pharmacokinetics (PK) of the proposed product were evaluated in Clinical study SFP-9, entitled "A double-blind, randomized, placebo-controlled, single ascending dose study of intravenously administered SFP in healthy volunteers. This study will be reviewed by the Clinical Pharmacology Reviewer at OCP. Since the PK profile of the proposed product was evaluated, this NDA submission does not include a BA/BE waiver request and therefore there is no biopharmaceutics information to be reviewed in this NDA

ONDQA CMC and Biopharmaceutics Filing Review and Initial Quality Assessment
NDA 206317 TRIFERIC® (ferric pyrophosphate) Solution
Rockwell Medical, Inc.

Issues Identified:
None

Filing Recommendation: Fileable.
From Biopharmaceutics perspective, NDA 206- 327 for Triferic™ soluble Ferric Pyrophosphate is fileable. Since there is no biopharmaceutics information to be reviewed in this NDA, no further action is warranted from the Biopharmaceutics perspective.

ONDQA CMC and Biopharmaceutics Filing Review and Initial Quality Assessment
NDA 206317 TRIFERIC® (ferric pyrophosphate) Solution
Rockwell Medical, Inc.

CMC FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
*	**If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.**			
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			N.A.

	Parameter	Yes	No	Comment
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
8.	Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		

	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
10	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		
24.	Does the section contain controls of the final drug product?	X		
25.	Has stability data and analysis been provided to support the requested expiration date?	X		
26.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
27.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
28.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
29.	If appropriate, is a separate microbiological section included assuring sterility of the drug product	X		

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
30.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

ONDQA CMC and Biopharmaceutics Filing Review and Initial Quality Assessment
NDA 206317 TRIFERIC® (ferric pyrophosphate) Solution
Rockwell Medical, Inc.

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	20-Sep-2013	--

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
31.	Has the draft package insert been provided?	X		
32.	Have the immediate container and carton labels been provided?	X		

J. BIOPHARMACEUTICS FILING PARAMETERS				
	Parameter	**Yes**	**No**	**Comment**
33.	Does the application contain dissolution data?		X	*The proposed drug products is a solution*
34.	Is the dissolution test part of the drug product specifications?			*Not Applicable (NA)*
35.	Does the application contain the dissolution method development report including data supporting the discriminating ability?			*NA*
36.	Is there a validation package for the analytical method and dissolution methodology?			*NA*
37.	Does the application include a biowaiver request?		X	
38.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development?			*NA*

39.	Are there any formulation and/or manufacturing changes implemented to the clinical formulation? If yes. Are data supporting the bridging between the clinical and commercial drug products and/or manufacturing sites?	X		(b) (4) [redacted] *The Applicant's statement above will be evaluated by the CMC Reviewer at ONDQA.*
40.	Is the proposed drug product a modified release dosage form (e.g., controlled release, delayed release)?		X	*NA*
41.	Does the application include an IVIVC model?		X	*NA*
42.	Does the application include information/data on the in vitro alcohol dose-dumping potential of the proposed drug product?		X	*NA*
43.	Is there enough information to assess the extended release designation claim?			*NA*
44.	Is there any in *vivo* BA or BE study in the submission?		X	

45.	Is the Biopharmaceutics team responsible of reviewing the *in vivo* BA or BE studies? If yes: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies)?		X	*NA*
46.	Is there any design space proposed using in vitro release as a response variable?		X	
47.	Is the control strategy related to in vitro drug release?		X	

BIOPHARMACEUTICS FILING CONCLUSION AND COMMENTS

	Parameter	Yes	No	Comment
48.	IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	X		
49.	If the NDA is not fileable from the Biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			NA
50.	Are there any potential review issues identified?		X	
51.	Are there any comments to be sent to the Applicant as part of the 74-Day letter?		X	
52.	Are there any internal comments for the other disciplines?	X		***The Applicant's statement about the*** (b) (4) ***will be evaluated by the CMC Reviewer.***

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

See appended electronic signature page}
Janice Brown M.S.
CMC Lead
Division 1
Office of New Drug Quality Assessment

{See appended electronic signature page}
Banu Zolnik, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

{See appended electronic signature page}
Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

{See appended electronic signature page}
Ali Al-Hakim, Ph.D.
Branch Chief
Division 1
Office of New Drug Quality Assessment

Initial Quality Assessment

SUMMARY

Soluble Ferric Pyrophosphate (SFP) is a mixed ligand iron compound in which iron (III) is bound to pyrophosphate and citrate. SFP is dissolved in hemodialysis concentrate used to generate hemodialysis solution so that patients receive it by diffusion across the dialyzer membrane during hemodialysis. (b) (4)

The applicant used two presentations of the Soluble Ferric Pyrophosphate (SFP) drug product in the clinical development program: ((b) (4) ; (2) SFP Concentrate. (b) (4) was used in the Phase 1/2 trials, whereas SFP Concentrate was used in the pivotal Phase 3 trials, CRUISE-1, CRUISE-2, and RMTI-SFP-6 (open-label phase). SFP Concentrate is the intended commercial presentation of the drug product for which the applicant describes in this NDA.

When used as recommended, patients will be dialyzed with solutions containing SFP with iron concentrations of 2 µM or 110 µg/L (b) (4)

SFP Concentrate is a clear, green or greenish-yellow, sterile solution containing 5.44 mg Fe/mL in 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 (SFP Concentrate) is admixed, (b) (4) with liquid bicarbonate concentrate (2.5 gal) (b) (4)

DRUG SUBSTANCE

1. The applicant provided virtually no physical and chemical information for their product. The following information was provided:

   Physical Description: Yellow to green powder
   Solubility: Soluble ferric pyrophosphate is readily soluble in water (>85 g/L). Soluble ferric pyrophosphate is completely insoluble in most organic solvents (MeOH, Acetone, THF, DMF, DMSO).

pH of 5% Solution in Water: A 5% solution in water exhibits a solution pH of about 6.
Chirality/Stereochemistry: Soluble Ferric Pyrophosphate contains no asymmetric centers and, therefore, no isomers/stereoisomers are possible

The applicant indicated that data was not available for the melting point range, pKa, pH solubility profile, particle size, partition coefficient, and hygroscopicity. This information is relatively easy to obtain and should be requested.

2. A complete list of the SFP drug substance manufacturing facilities is appended as attachment 1. SFP is manufactured by (b) (4)

3. SFP is manufactured by (b) (4) The synthetic scheme is reproduced in attachment 3.

(b) (4) In a meeting with the applicant on 26-Nov-2013, the agency agreed that these materials could be designated as starting materials provided that adequate data was submitted to support the structure of SFP.

4. The drug substance specification is appended in attachment 4. Note that the drug substance specification does not include a test for (b) (4) which is an impurity in other iron products. In addition, a limit should also be considered for (b) (4) since testing is performed using this methodology but no acceptance criterion is proposed.

5. Impurities:

   5.1 Organic Impurities: No actual or potential organic impurities have been identified.

   5.2 Inorganic impurities: Heavy metals are determined using Inductively Coupled Plasma – Mass Spectroscopy (ICP-MS) method and are controlled in the drug substance at the limits listed in table 1.

Table 1: Elemental Impurities (Heavy Metals) in SFP.

Test Parameter	Specifications	Procedure Reference	USP 232 limit for parenteral DP with a max daily dose ≤10g/day	ICH Q3D PDE
(b) (4)	NMT (b) (4) µg/g	Coupled Plasma – Mass Spectroscopy – USP <232> and USP <233> 505094001 - ICPMS	No requirement	
	NMT g/g		No requirement	
Arsenic	NMT g/g		0.15 µg/g	15 µg/day
(b) (4)	NMT µg/g		No requirement	
	NMT g/g		No requirement	
Cadmium	NMT g/g		0.25 µg/g	15 µg/day
Copper	NMT µg/g		10 µg/g	
Lead	NMT g/g		0.5 µg/g	5 µg/day
Mercury	NMT g/g		0.15 µg/g	
(b) (4)	NMT g/g		No requirement	
	NMT g/g		No requirement	

(b) (4) Rockwell has provided a justification explaining that the limits for heavy metal contaminants in SFP drug substance will not exceed (b) (4)% of the AAMI, ISO, and EP water limits. Since the USP does not have a monograph for this product, USP <232> would not apply the drug substance or drug product. Consider requesting testing for elemental impurities in the drug product to ensure levels comply with Q3D.

Note that USP <232> also has limits for elemental impurities for the drug products since heavy metals may be introduced inadvertently (e.g., (b) (4)); however, implementation of <232> has been deferred to December 1, 2015.

As a background, currently most manufacturer's rely on general chapter <231> Heavy Metals which applies only to active pharmaceutical ingredients and excipients. USP<231> is a limit test based on the sum of the 10 elements, and so does not give individual concentrations for each individual element. USP General Chapter <231> will be omitted once general Chapters <231> and <232> become applicable on December 1, 2015. The removal of references to <231> from USP-NF monographs also will be official as of December 1, 2015.

5.3 Residual solvents: (b) (4)

(b) (4)
.

6. Container – Closure: (b) (4) for soluble ferric pyrophosphate drug substance is a (b) (4) . The application did include a description of the container closure system; however the composition of the (b) (4) was not provided. (b) (4) . Recommend requesting this information to be submitted in the application or alternatively they could submit a LOA referencing a DMF for the materials used in the manufacture of the (b) (4)

(b) (4)

7. Stability: The applicant submitted 12 months of long-term and 6 months of accelerated stability data for 4 batches of drug substance. Tables 2 and 3 include batch information and the stability data, respectively. Note that batches 0804536, 0804537, and 0804538 were stored (b) (4) and batch 1004939 was stored (b) (4)

Table 2: Drug Substance Batches Tested

Batch Number	**Date of Manufacture**	**Manufacturing Location**	**Batch Size**	**Type of Batch**
0804536	24-Jan-2008	(b) (4)	(b) (4)	Commercial
0804537	04-Feb-2008			Commercial
0804538	04-Feb-2008			Commercial
1004939	21-Dec-2010		Not provided in batch analysis	--

Table 3: Long term stability and accelerated testing

Batch	Storage Condition	Testing Schedule	Amount of data in the NDA	Purpose
0804536	25˚C/60%RH	1, 3, 6, 9, 12, 18, 24, 36, 48, 60 mos.	60 mos.	Long term stability
0804537	25˚C/60%RH	1, 3, 6, 9, 12, 18, 24, 36, 48, 60 mos.	60 mos.	
0804538	25˚C/60%RH	1, 3, 6, 9, 12, 18, 24, 36, 48, 60 mos.	60 mos.	
1004939	25˚C/60%RH	1, 3, 6, 9, 12, 18, 24, 36, 48, 60 mos.	24 mos.	
0804536	30˚C/75%RH	1, 3, 6, 9, 12 mos.	0 mos.	Intermediate conditions
0804537	30˚C/75%RH	1, 3, 6, 9, 12 mos.	0 mos.	
0804538	30˚C/75%RH	1, 3, 6, 9, 12 mos.	0 mos.	
1004939	30˚C/75%RH	1, 3, 6, 9, 12 mos.	0 mos.	
0804536	40˚C/75%RH	0, 3, 6 mos.	6 mos.	Accelerated conditions
0804537	40˚C/75%RH	0, 3, 6 mos.	6 mos.	
0804538	40˚C/75%RH	0, 3, 6 mos.	6 mos.	
1004939	40˚C/75%RH	0, 3, 6 mos.	6 mos.	

7.1 Stability results for batches 0804536, 0804537, and 0804538 (b) (4) when stored under long term conditions. These batches also (b) (4) under accelerated conditions at (b) (4). Results for (b) (4) were at or near the proposed limit of (b) (4)% w/w. As a result of these failures, (b) (4). Batch 1004939 was packaged with the (b) (4) met the proposed limits under long term and accelerated conditions.

Surprisingly, the applicant requested a retest date of (b) (4) months. According to Q1E if a significant change occurs at the intermediate condition, the proposed retest period or shelf life should not exceed the period covered by long-term data. In addition, a retest period or shelf life shorter than the period covered by long-term data could also be considered.

Since the results at (b) (4) months were at the (b) (4) content limit of NMT (b) (4)% under long term conditions and failed the same attribute at (b) (4) months under accelerated conditions, a (b) (4) month shelf life is certainly reasonable.

7.2 Forced Degradation Studies: Forced degradation studies were conducted as part of the ion chromatography assay method validation to characterize the degradation profile of the drug substance under various stress conditions (b) (4)

(b) (4) and to demonstrate that the method is stability indicating.

(b) (4)

7.3 (b) (4)

DRUG PRODUCT

8. SFP Concentrate is a clear, green or greenish-yellow, sterile solution containing 5.44 mg Fe/mL in Water for Injection, USP, packaged in 5 mL (b) (4) low density polyethylene (LDPE) (b) (4) ampoule. At the time of use, the drug product is admixed, (b) (4) with liquid bicarbonate concentrate (2.5 gal) (b) (4)

9. The quantitative composition of SFP is reproduced in table 4 below.

Table 4: Composition of the SFP Concentrate Drug Product

Ingredients	**Function**	**Quality Standard**	**Unit (5 mL) Composition Strength (label claim): 5.44 mg Fe/mL**	
			Quantity	**Percent**
Soluble Ferric Pyrophosphate (SFP)	Active Ingredient	Reference Standard	27.2 mg Fe[a] (w/w)	0.544% (w/w)
Water for Injection	(b) (4)	USP/Ph.Eur.	q.s. to volume	-
Total			5 mL	100.00% (w/w)

[a] Iron (Fe) content of SFP is 7.5% - 9.0% w/w, (b) (4)

10. SFP Concentrate is manufactured by (b) (4) A complete list of manufacturing facilities is appended in attachment 2.

11. The SFP manufacturing flow diagram is reproduced in attachment 4. SFP is manufactured by (b) (4) that includes:

(b) (4)

12. The drug product release and stability specification are reproduced in attachments 5 and 6. These specifications should be combined into a single drug product specification. According to ICH Q6A, there are universal tests that are considered to be applicable to all new drug products. These tests include appearance, identification, assay, and impurity. Note that the applicant does not perform impurity (heavy metals) monitoring or content uniformity. Consider requesting this information or a justification why it is not performed.

13. According to the applicant, (b) (4) is an impurity that is monitored and controlled. Consider requesting an addition test for (b) (4) or a justification why testing is not routinely performed.

    Also elemental impurities are not tested. Consider requesting testing for elemental impurities in the drug product to insure levels comply with Q3D.

14. The primary packaging of SFP Concentrate is a (b) (4) ampoule made from (b) (4) a low density polyethylene (LDPE). The DMF Letter of Authorization for LDPE was provided.

    14.1 The primary packaging of SFP Concentrate is a (b) (4) ampoule made from (b) (4) a low density polyethylene (LDPE). There are no ink imprints or other adhesives on the outside of the primary container. According to the applicant, (b) (4) meets the following requirements:

(b) (4)

(b) (4)

- According to the container closure guidance an extraction study on the packaging component should be performed to determine which chemical species may migrate into the dosage form (and at what concentration); and, second, a toxicological evaluation of those substances which are extracted to determine the safe level of exposure via the label specified route of administration.

14.2 While the applicant performed an extraction profile, there was no toxicological evaluation. Recommend producing a table listing all the extractables along with the concentration (b) (4) and forward this information to the nonclinical reviewer for their evaluation.

15. Drug Product Stability Studies: The applicant submitted 30 months of long term stability data at 25°C/60% RH and 6 months at accelerated storage conditions at 40°C/75% RH for four primary batches (LP 174, ME 020, ME 023, and NE 332) of drug product. All four batches were packaged in 5 mL low density polyethylene (LDPE) ampoules, which is the proposed commercial primary package. In addition, the LDPE ampoules of batch NE 332 were packaged in a pouch made of aluminum foil laminate, the intended secondary container for commercialization. All stability studies are ongoing to cover the proposed (b) (4) month retest period.

15.1 Summarized in table 5 is the stability batch information in the NDA.

Table 5: Description of batches tested

DP batch no.	Date of man.	Batch size	Site of man.	Storage Conditions	Testing Schedule	Amount of data in the NDA
LP174	21-Dec-2010		(b) (4)	25˚C/60%RH	0, 1, 2, 3, 6, 9, 12, 18, 24, 30 mos.	30 mos.
				40˚C/75%RH	0, 1, 2, 3, 6 mos.	6 mos.
ME020	03-Mar-2011			25˚C/60%RH	0, 1, 2, 3, 6, 9, 12, 18, 24, 30 mos.	30 mos.
				40˚C/75%RH	0, 1, 2, 3, 6 mos.	6 mos.
ME023	04-Mar-2011			25˚C/60%RH	0, 1, 2, 3, 6, 9, 12, 18, 24, 30 mos.	30 mos.
				40˚C/75%RH	0, 1, 2, 3, 6 mos.	6 mos.
NE332	05-Apr-2012			25˚C/60%RH	0, 1, 2, 3, 6, 9, 12, 18, 24, 30 mos.	12 mos.
				40˚C/75%RH	0, 1, 2, 3, 6 mos.	6 mos.

Results for all four lots packaged in packaged in the proposed commercial primary container, 5 mL low density polyethylene (LDPE) ampoules are within specification after 30 months under the long-term storage conditions of 25°C/60%RH and 6 months of accelerated conditions at 40˚C/75% RH. Note that (b) (4) was at the proposed limit for all batches under long term conditions.

15.2 The applicant is requesting (b) (4) month shelf life based on 30 months of long term data which is certainly reasonable.

15.3 A photostability study was carried out according to ICH Q1B that shows the SFP drug product is light sensitive. Section 16.2 of the proposed labeling states that the product should be stored in an aluminum pouch.

15.4 The applicant performed an in-use study was to determine the stability of SFP in bicarbonate concentrate under ambient conditions over a twelve week period. (b) (4) Samples were tested at initial, 1 week, 3 weeks, 6 weeks, 9 weeks and 12 weeks after preparation.

(b) (4) however, no scientific data was presented to support their conclusion. A similar study was performed on the compatibility of SFP with dialysate and dialyzers.

Consider requesting a justification for determining acceptable results for both admix studies. (b) (4) .
If it does not represent actual use the validity of these studies are questionable. Further discussion with the CDRH consult regarding the actual in-use conditions may be helpful.

Attachment 1: SFP Drug Substance Manufacturing Sites

Site/address	DUNS/FEI1	Responsibilities
(b) (4)		• Manufacture • Bulk Packaging • Stability Testing • Release Testing • Release
		• Release Testing • Stability Testing

Attachment 2: SFP Drug product sites

Site	DUNS/ FEI[1]	Responsibility
(b) (4)		Site 1: • (b) (4) filling/primary packaging • Secondary packaging • Labeling
		• (b) (4)
		• Release testing of final dosage form and stability testing - Appearance - Identification - Assay - pH - Endotoxins - Sterility

Attachment 3: Ferric Pyrophosphate Synthetic Scheme

Figure 3.2.S.2.2-1. Summary of Soluble Ferric Pyrophosphate Synthetic Process

Attachment 4: SFP Drug Substance Specification

Table 2.3.S.4-1. Specifications and Tests of Soluble Ferric Pyrophosphate

Test Parameter	Specifications	Procedure Reference
Appearance by visual inspection	Yellow to green powder	505094001 - DESC
Identification - Ferric Iron by Inductively Coupled Plasma - Optical Emission Spectroscopy	Conforms	505094001 - FeID
Identification - Pyrophosphate by Ion Chromatography	Conforms	505094001 - ICID
Assay by Ion Chromatography (b) (4)	(b) (4) (b) (4)	505094001 505094001 505094001 505094001 505094001 (b) (4)
Iron Content by Inductively Coupled Plasma - Optical Emission Spectroscopy	Report only, % w/w as is	505094001 - ICPOES
Loss on Drying – USP <731>	NMT (b) (4) % w/w	505094001 - LOD
(b) (4)	(b) (4) % w/w	505094001 - (b) (4)
Solubility (10% conc./H_2O)	Conforms	505094001 - SOLUB
Microbial Limit Tests – Total Aerobic Count, Total Molds and Yeast - USP <61>	Total Aerobic Count LT (b) (4) CFU/g Total Molds and Yeasts L CFU/g	505094001 - MICROB

Test Parameter	Specifications	Procedure Reference
Heavy Metals by Inductively Coupled Plasma – Mass Spectroscopy – USP <232> and USP <233>		505094001 - ICPMS
(b) (4)	NMT (b) (4) µg/g NMT µg/g NMT µg/g NMT µg/g NMT µg/g NMT µg/g NMT µg/g NMT µg/g NMT µg/g NMT µg/g NMT µg/g	
Bacterial Endotoxin – USP <85> (Method LAL gel clot method)	(b) (4)	505094001 - BACT

Abbreviations: (b) (4) LT = less than, NMT = not more than, w/w = weight/weight.

Attachment 4: SFP Drug Product Manufacturing Flow Diagram

Figure 3.2.P.3.3- 1. Manufacturing Process of SFP Concentrate

Attachment 5: Drug Product Release Specification

SFP Concentrate Specifications – Release

Specification: 00
Supersedes: None
Manufacturer: (b) (4)

Effective Date: May 16, 2013
Manufacturing Location: (b) (4)

Test	Acceptance Criteria	Analytical Procedure (Type and Source)
Appearance	Green or greenish yellow solution	Visual/House
Identification Iron	Conforms	USP <191>
Identification Pyrophosphate and Citrate	Conforms	Ion Chromatography with electrochemical detection/M6767
Assay Iron	(b) (4) mg Fe/mL	Titrimetry/M6766
Assay Anion content	Citrate: (b) (4) mg/mL Phosphate: (b) (4) mg/mL Pyrophosphate: (b) (4) mg/mL Sulfate: (b) (4) mg/mL	Ion Chromatography with electrochemical detection/ M6767
pH	(b) (4)	USP<791>
Fill Volume	(b) (4) mL	USP<755>
Sterility	Sterile	USP<71>
Endotoxin	(b) (4) EU/mL	USP<85>

NMT = not more than; NLT = not less than

Attachment 6: Drug Product Stability Specification

SFP Concentrate Specifications – Stability

Specification: 00
Supersedes: None
Manufacturer (b) (4)

Effective Date:
Manufacturing Location: (b) (4)

Test	Acceptance Criteria	Analytical Procedure (Type and Source)
Appearance	Green or greenish yellow solution	Visual/House
Identification Iron	Conforms	USP <191>
Identification Pyrophosphate and Citrate	Conforms	Ion Chromatography with electrochemical detection/M6767
Assay Iron	(b) (4) mg Fe/mL	Titrimetry/M6766
Assay Anion content	Citrate: (b) (4) mg/mL Phosphate: (b) (4) mg/mL Pyrophosphate; (b) (4) mg/mL Sulfate; (b) (4) mg/mL	Ion Chromatography with electrochemical detection/M6767
pH	(b) (4)	USP<791>
Sterility	Sterile	USP<71>
Endotoxin	(b) (4) EU/mL	USP<85>

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/s/

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