CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206317Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 206317 SUPPL # HFD #

Trade Name Triferic

Generic Name ferric pyrophosphate citrate

Applicant Name Rockwell Medical, Inc.

Approval Date, If Known January 23, 2015

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#	021135	Venofer (iron sucrose injection, USP)
NDA#	020995	Ferrlecit (sodium ferric gluconate complex)
NDA #	022180	Feraheme (ferumoxytol)
NDA#	203565	Injectafer (ferric carboxymaltose) injection
NDA#	017441	INFeD (iron dextrane injection, USP)

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

RMTI-SFP-4
A Randomized, Placebo-Controlled, Phase 3 Study of Dialysate Containing Soluble Ferric Pyrophosphate (SFP) in Chronic Kidney Disease Patients Receiving Hemodialysis: The Continuous Replacement Using Iron Soluble Equivalents (CRUISE 1) Study

RMTI-SFP-5
A Randomized, Placebo-Controlled, Phase 3 Study of Dialysate Containing Soluble Ferric Pyrophosphate (SFP) in Chronic Kidney Disease Patients Receiving Hemodialysis: The Continuous Replacement Using Iron Soluble Equivalents (CRUISE 2) Study

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☒	NO ☐
Investigation #2	YES ☒	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

RMTI-SFP-4
A Randomized, Placebo-Controlled, Phase 3 Study of Dialysate Containing Soluble Ferric Pyrophosphate (SFP) in Chronic Kidney Disease Patients Receiving Hemodialysis: The Continuous Replacement Using Iron Soluble Equivalents (CRUISE 1) Study

RMTI-SFP-5
A Randomized, Placebo-Controlled, Phase 3 Study of Dialysate Containing Soluble Ferric Pyrophosphate (SFP) in Chronic Kidney Disease Patients Receiving Hemodialysis: The Continuous Replacement Using Iron Soluble Equivalents (CRUISE 2) Study

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

RMTI-SFP-4
A Randomized, Placebo-Controlled, Phase 3 Study of Dialysate Containing Soluble Ferric Pyrophosphate (SFP) in Chronic Kidney Disease Patients

Receiving Hemodialysis: The Continuous Replacement Using Iron Soluble Equivalents (CRUISE 1) Study

RMTI-SFP-5
A Randomized, Placebo-Controlled, Phase 3 Study of Dialysate Containing Soluble Ferric Pyrophosphate (SFP) in Chronic Kidney Disease Patients Receiving Hemodialysis: The Continuous Replacement Using Iron Soluble Equivalents (CRUISE 2) Study

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 51290	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 51290	YES ☒	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!

YES ☐	NO ☐
Explain:	Explain:
Investigation #2	
YES ☐	NO ☐
Explain:	Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Amy Chi
Title: Regulatory Project Manager
Date: January 23, 2015

Name of Office/Division Director signing form: Ann T. Farrell, MD
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

AMY H CHI
01/23/2015

ANN T FARRELL
01/23/2015

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 206317 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name:DHP PDUFA Goal Date: January 24, 2014 Stamp Date: March 24, 2014

Proprietary Name: Triferic

Established/Generic Name: soluble ferric pyrophosphate

Dosage Form: _____

Applicant/Sponsor: Rockwell Medical, Inc.

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Iron replacement product for the treatment of iron loss and maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease.

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☐ indication(s); ☒ dosage form; ☐ dosing regimen; or ☒ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☒ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☒ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible[#]	Not meaningful therapeutic benefit[*]	Ineffective or unsafe[†]	Formulation failed[Δ]
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☒	Other	0 yr. 0 mo.	17 yr. 11 mo.	☒	☐	☐	☒
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): June, 2021						

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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

/s/

AMY H CHI
12/18/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 206317 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Triferic Established/Proper Name: ferric pyrophosphate citrate Dosage Form: 5.44 mg Fe/mL		Applicant: Rockwell Medical, Inc. Agent for Applicant (if applicable):
RPM: Amy Chi		Division: Division of Hematology Products

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is January 24, 2014	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 5
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Version: 5/14/2014

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval 1/23/2015
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included 3/24/2014
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Letter 6/26/2014 Review 6/24/2014
❖ Labeling reviews *(indicate dates of reviews)*	RPM: 5/23/2014 DMEPA: 10/2/2014 DMPP/PLT (DRISK): ☒ None OPDP: 11/20/2014 SEALD: ☒ None CSS: ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	5/23/2014 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 11/12/2014 If PeRC review not necessary, explain: _____	12/18/2014 Pediatric Page 11/12/2014 PeRC Meeting Minutes 10/27/2014 PeRC Template
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	1/23/15 (3); 1/22/15; 1/16/15; 1/15/15; 1/9/15; 12/22/14 (2); 12/18/14; 12/12/14; 11/2/14; 10/28/14; 10/23/14; 10/22/14; 10/14/14; 10/10/14 (2); 10/8/14; 10/7/14; 10/6/14; 10/3/14; 9/30/14 (2); 9/26/14; 9/18/14; 9/16/14; 8/21/14; 8/15/15; 8/13/14 (2); 8/7/14; 8/4/14; 7/31/14; 7/2/14 (2); 6/30/14; 6/18/14; 6/2/14; 5/27/14 (2); 5/15/14; 4/28/14; 4/23/14; 4/4/14; 3/31/14 (2)
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	8/11/14 Telecon minutes
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	11/26/2013 (CMC) and 9/9/2013
• EOP2 meeting *(indicate date of mtg)*	6/30/2010
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	11/6/2014
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	1/23/2015
Cross-Discipline Team Leader Review *(indicate date for each review)*	1/26/2015
PMR/PMC Development Templates *(indicate total number)*	2
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review Co-signed 12/19/2014 review
• Clinical review(s) *(indicate date for each review)*	Primary Review 12/19/2014 Filing Review 5/16/2014

Version: 5/14/2014

• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Refer to page 15 of Clinical Primary Review dated 12/19/2014
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	DCRP review 10/17/2014
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	DRISK Review 12/16/2014
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	Review 11/24/2014 Letters: 12/1/2014; 11/22/2014; 11/17/2014; 10/8/2014; 9/10/2014
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review Co-signed 12/24/2014 review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review Co-signed 12/24/2014 review
Statistical Review(s) *(indicate date for each review)*	Primary Review 12/24/2014 Filing Review 5/14/2014
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review Co-signed 12/11/2014 review
Clinical Pharmacology review(s) *(indicate date for each review)*	Primary Reviews 12/11/2014 and 4/28/2014 Filing Review 5/23/2014
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	12/23/2014
• Supervisory Review(s) *(indicate date for each review)*	12/22/2014
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	Primary Review 12/22/2014 Filing Review 5/16/2014
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ No separate review
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ No separate review Co-signed 1/22/2015 and 12/17/2014 reviews
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	Reviews 1/22/2015; 12/17/2014 and 8/18/2014 Filing Review 5/21/2014
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	Primary Review12/3/2014 Filing Review 4/23/2014
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	Refer to page 85 of CMC primary review dated 12/17/2015
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: 12/1/2014 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable Filing review 5/23/2014
☐ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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/s/

PATRICIA N GARVEY
01/30/2015

Chi, Amy H

From: Chi, Amy H
Sent: Friday, January 23, 2015 12:00 PM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: RE: NDA 206317 (Triferic) - FDA Proposed PI
Attachments: RFI 23 January 2015 Annotations and Responses to FDA Proposed Label for Triferic 23 Jan 2015.docx

Importance: High

Dear Dr. Pratt,

In response to your email sent today, January 23, 2014, please see the FDA's response to Rockwell's proposed annotation:

FDA response:

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

Please let me know if you have any questions. Please provide a response by 1:00 PM today.

Thank you,

Amy

From: Ray Pratt [mailto:rpratt@rockwellmed.com]
Sent: Friday, January 23, 2015 11:23 AM
To: Chi, Amy H
Subject: RE: NDA 206317 (Triferic) - FDA Proposed PI - Due January 23rd

Cdr. Chi

Attached is Rockwell's response to the 2 Questions sent earlier today.

Please send FDA's response so I can incorporate in the final draft label.

Thank you

Raymond D. Pratt, MD FACP
Chief Medical Officer

Rockwell Medical
30142 S. Wixom Rd.
Wixom, MI 48393
248-960-9009
www.rockwellmed.com

4 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

AMY H CHI
01/23/2015

Chi, Amy H

From: Chi, Amy H
Sent: Friday, January 23, 2015 9:36 AM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: RE: NDA 206317 (Triferic) - FDA Proposed PI - Due January 23rd

Importance: High

Good morning Dr. Pratt,

The Division has an additional comment to Rockwell's proposed PI sent yesterday, January 22nd. Please see FDA comment below of what the Division is proposing to accept:

14 CLINICAL STUDIES

The safety and efficacy of Triferic in patients with HDD-CKD was assessed in two randomized, single blind, placebo-controlled clinical trials. Patients with hemoglobin of 9 g/dL to 12 g/dL with TSAT >20% and serum ferritin concentrations > 200 mcg/L were enrolled. Patients were to remain in randomized treatment until pre-specified hemoglobin or ferritin criteria were met, indicating the need for a change in anemia management or if they completed 48 weeks. Triferic was added to bicarbonate concentrate with a final concentration of 110 mcg iron/L in the dialysate and was administered 3 or 4 times per week during hemodialysis. Most patients were receiving stable dose of erythropoiesis stimulating agents (ESAs) at baseline. After randomization, (b) (4) patients' ESA doses were not to (b) (4) be changed .

Please let me know if you have any questions.

Thanks,

Amy

From: Chi, Amy H
Sent: Friday, January 23, 2015 8:57 AM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: FW: NDA 206317 (Triferic) - FDA Proposed PI - Due January 23rd
Importance: High

Good morning Dr. Pratt,

Please refer to your email (below) dated January 22, 2015. The Division has reviewed Rockwell's proposed comments to the PI and we do not agree with your responses. Please provide justification to address FDA comment # A3 below:

FDA's Comment (A3): To Rockwell: (b) (4)

Please provide a timely response by 2:00pm today.

Thank you,

Amy

From: Ray Pratt [mailto:rpratt@rockwellmed.com]
Sent: Thursday, January 22, 2015 5:01 PM
To: Chi, Amy H
Subject: RE: NDA 206317 (Triferic) - FDA Proposed PI - Due January 23rd

Cdr. Chi

Rockwell's edits to draft PI.

We have accepted most of FDA's proposals. Please see the following comment balloons which need resolution.

Comment A9: Indication: (b) (4)

Comment A13: (b) (4) (b) (4).

Comment A34/A35: (b) (4) We propose the following:

(b) (4)

Please give me a call tomorrow AM to discuss so we can finalize the PI.

Thank you

Raymond D. Pratt, MD FACP
Chief Medical Officer

Rockwell Medical
30142 S. Wixom Rd.
Wixom, MI 48393
248-960-9009
www.rockwellmed.com

From: Chi, Amy H [mailto:Amy.Chi@fda.hhs.gov]
Sent: Thursday, January 22, 2015 3:15 PM
To: Ray Pratt
Subject: NDA 206317 (Triferic) - FDA Proposed PI - Due January 23rd

Dear Dr. Pratt,

Please see attached revised draft of the PI for NDA 206317.

Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)

After you have made the changes, please send me the revised PI in tracked change before you make your official submission electronically.

Please provide a revised PI to me by **9:00 AM Friday, January 23, 2015.**

Please contact me if you have any questions,

Kind regards,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
01/23/2015

Chi, Amy H

From: Chi, Amy H
Sent: Friday, January 23, 2015 8:57 AM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: FW: NDA 206317 (Triferic) - FDA Proposed PI - Due January 23rd
Attachments: NDA 206317_Triferic_draft-labeling-text-word_Rockewll's proposed edits sent to FDA_ 1.22.15.doc

Importance: High

Good morning Dr. Pratt,

Please refer to your email (below) dated January 22, 2015. The Division has reviewed Rockwell's proposed comments to the PI and we do not agree with your responses. Please provide justification to address FDA comment # A3 below:

FDA's Comment (A3): To Rockwell: (b) (4) .

Please provide a timely response by 2:00pm today.

Thank you,

Amy

From: Ray Pratt [mailto:rpratt@rockwellmed.com]
Sent: Thursday, January 22, 2015 5:01 PM
To: Chi, Amy H
Subject: RE: NDA 206317 (Triferic) - FDA Proposed PI - Due January 23rd

Cdr. Chi

Rockwell's edits to draft PI.

We have accepted most of FDA's proposals. Please see the following comment balloons which need resolution.

Comment A9: Indication: (b) (4)

Comment A13: (b) (4) .

Comment A34/A35: (b) (4) We propose the following:

(b) (4)

Please give me a call tomorrow AM to discuss so we can finalize the PI.

Thank you

Raymond D. Pratt, MD FACP
Chief Medical Officer

Rockwell Medical
30142 S. Wixom Rd.
Wixom, MI 48393
248-960-9009
www.rockwellmed.com

From: Chi, Amy H [mailto:Amy.Chi@fda.hhs.gov]
Sent: Thursday, January 22, 2015 3:15 PM
To: Ray Pratt
Subject: NDA 206317 (Triferic) - FDA Proposed PI - Due January 23rd

Dear Dr. Pratt,

Please see attached revised draft of the PI for NDA 206317.

Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)

After you have made the changes, please send me the revised PI in tracked change before you make your official submission electronically.

Please provide a revised PI to me by **9:00 AM Friday, January 23, 2015.**

Please contact me if you have any questions,

Kind regards,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
01/23/2015

Chi, Amy H

From: Chi, Amy H
Sent: Thursday, January 22, 2015 3:15 PM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: NDA 206317 (Triferic) - FDA Proposed PI - Due January 23rd
Attachments: NDA 206317_Triferic_draft-labeling-text-word_FDA proposed edits sent to Rockwell_1.22.15.doc

Importance: High

Dear Dr. Pratt,

Please see attached revised draft of the PI for NDA 206317.

Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)

After you have made the changes, please send me the revised PI in tracked change before you make your official submission electronically.

Please provide a revised PI to me by **9:00 AM Friday, January 23, 2015.**

Please contact me if you have any questions,

Kind regards,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
01/22/2015

Chi, Amy H

From: Chi, Amy H
Sent: Friday, January 16, 2015 12:02 PM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: RE: FDA RESPONSE: NDA 206317 (Triferic) - FDA Proposed Carton Container/Ampule Label - Due January 19th
Attachments: NDA 206317 draft-carton-labeling.pdf; NDA 206317 draft-carton-labeling-callouts.pdf; NDA 206317 secondary-pouch-label-including-callouts.pdf; NDA 207317 secondary-pouch-label.pdf; NDA 2063173303b_j15b60_drw b.pdf

Importance: High

Dear Dr. Pratt,

Please reference NDA 206317 for Triferic®, submitted March 24, 2014. FDA has reviewed Rockwell's proposed responses to the carton container/ampule. We have accepted the proposed editorial changes with the exception of the following comments.

FDA Comments:

Regarding the ampule label submitted in an email dated 12 Jan 2015:

1. The drug name should be listed as "Triferic"; delete (b) (4) since the (b) (4) .
2. (b) (4)

Regarding the pouch and carton labels submitted in amendment S-043 dated 29 Dec 2014:

3. Revise the drug established name from (b) (4) to "triferic pyrophosphate citrate". This is the name accepted by the USAN nomenclature committee on 09 Jan 2015.

Please address these items in a revised carton container/ampule label and send to me by **2:00 PM Monday, January 19, 2014**. Please formally submit the revised labels to the NDA file by January 19, 2015.

Please confirm receipt of this message.

Please contact me if you have any questions,

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
01/16/2015

Chi, Amy H

From: Chi, Amy H
Sent: Thursday, January 15, 2015 6:16 PM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: NDA 206317 (Triferic) - FDA Proposed PI - Due January 19th
Attachments: NDA 206317_Triferic_draft-labeling-text-word_FDA Proposed Edits_sent to Rockwell_1.15.15.doc

Importance: High

Dear Dr. Pratt,

Please see attached revised draft of the PI for NDA 206317.

Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)

After you have made the changes, please send me the revised PI in tracked change before you make your official submission electronically.

Please provide a revised PI to me by **2:00 PM Monday, January 19, 2014**.

Please contact me if you have any questions,

Kind regards,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
01/15/2015

Chi, Amy H

From: Chi, Amy H
Sent: Friday, January 09, 2015 12:35 PM
To: Ray Pratt (rpratt@rockwellmed.com); Carrie Guss (cguss@rockwellmed.com)
Subject: RE: RESPONSE NEEDED: Statistical Informational Request: NDA 206317: Triferic
Attachments: sfp4-sfp5-report-body.pdf

Sorry, I forgot to include the attachment.

Thanks,

Amy

From: Chi, Amy H
Sent: Friday, January 09, 2015 12:34 PM
To: Ray Pratt (rpratt@rockwellmed.com); Carrie Guss (cguss@rockwellmed.com)
Subject: RESPONSE NEEDED: Statistical Informational Request: NDA 206317: Triferic
Importance: High

Dear Dr. Pratt,

Please reference NDA 206317 for Triferic, submitted March 24, 2014 and Rockwell's proposed PI submitted on December 29, 2014. We would like to request a prompt response to the following Statistical Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Information Request:

1. Please explain why the numbers for the secondary endpoints (ferritin, CHr, TSAT) in the ITT population in Table 3 of the proposed PI are different from the submission on October 16 which is intended to be the results based on ITT population. See attached.

2. Please also clarify how the numbers from Table 3 of the proposed PI were calculated including any data imputation method used. Based on FDA's review, the numbers for the secondary endpoints in the ITT population in table 3 are from information submitted around Aug 12 (please confirm), but for change from baseline to EOT values, they are the same as the original submission for the MITT population."

Please respond to this Information Request to me by email by **12:00 noon Monday, January 12, 2015**. You will need to also officially submit the information to your NDA.

Please confirm receipt of this message.

Kind regards,

Amy

Amy Chi, MSN

CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
01/09/2015

Jones, Jacquin

From: Jones, Jacquin
Sent: Monday, December 22, 2014 1:17 PM
To: 'rpratt@rockwellmed.com'
Cc: Chi, Amy H
Subject: FDA RESPONSE:NDA 206317: FDA Proposed Carton Labeling for Triferic: Due by January 5th

Good afternoon Dr. Pratt,

Please reference NDA 206317 for Triferic®, submitted March 24, 2014. FDA has reviewed your clarification request concerning the (b) (4) requirements and provides the following response to the (b) (4) Label (proposed carton labeling) inquiry.

FDA Comments:

- We understand the desire to maximize the trade name and the product owner's name. However, certain information is necessary for the immediate container. Although there is no requirement for a storage statement, the product is light sensitive and should not be left on the counter, thus we request that a storage statement be present. The numbers on the bottom of the ampule are available for use as a lot# (b) (4) and expiry date or product code (b) (4)

- Based upon the information you have previously provided, we propose the following:
  FRONT
  Rx (anywhere on the front)
  Triferic (established name) (b) (4)
  27 mg Fe(III)/ 5 mL
  Keep ampule in pouch until use (or a shorter version)

- BACK
  Manufactured for … or Distributed by Rockwell Medical Inc.
  Lot number (this can be anywhere on the ampule as long as it is clearly visible)

Please respond to this correspondence and the previous December 18, 2014 Information Request via email by **10:00 AM ET, Monday January 5, 2015**. Also, please officially submit all responses, documents and information to the NDA file.

Please confirm receipt of this message; and cc me on all replies as I am covering for Amy Chi this week.

Have a good day,

Jackie

Jacquin L. Jones, CDR, MS, RN, USPHS
Regulatory Health Project Manager
Division of Hematology Products
OHOP/CDER/FDA
10903 New Hampshire Ave, Bldg 22, RM 2222

Silver Spring, MD 20903
Tel: 240-402-4590, Fax: 301-796-9909

APPEARS THIS WAY ON ORIGINAL

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/s/

JACQUIN L JONES
12/22/2014

Chi, Amy H

From: Chi, Amy H
Sent: Monday, December 22, 2014 7:19 AM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: RE: PMRs for Triferic: NDA 206317

Importance: High

Dear Dr. Pratt

Please reference your NDA for Triferic, NDA 206317, submitted March 24, 2014.

As we continue our review of your Application, our normal policy is to consider post-marketing studies and labeling at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs) based on the data available to date. We may have additional PMRs/PMCs later. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. It is also necessary for you to provide schedule milestone dates as indicated. We consider the proposed milestone dates listed below to be feasible but rather generous.

We are available to discuss by teleconference, if needed.

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR trial description to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial.

Final PMR designation numbers will be assigned later.

PMR #1:

PMR Description: Efficacy and safety trial of Triferic via hemodialysate in pediatric patients aged less than 18 years with hemodialysis-dependent chronic kidney disease.

PMR Schedule Milestones:		
	Final Protocol Submission:	03/31/2018
	Trial Completion:	07/31/2020
	Final Report Submission:	12/31/2020
	Other:	

PMR #2:

PMR Description: Submit the final report for the pediatric pharmacokinetic trial entitled "Pharmacokinetics of SFP iron delivered via dialysate in pediatric patients with chronic kidney disease on hemodialysis".

PMR Schedule Milestones:		
	Final Protocol Submission:	03/31/2015

Trial Completion:	02/28/2017
Final Report Submission:	06/30/2017
Other:	

Please officially submit the responses to NDA 206317 and also email to me.

Please confirm receipt.

Kind regards,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
12/22/2014

Chi, Amy H

From: Chi, Amy H
Sent: Thursday, December 18, 2014 1:37 PM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: RESPONSE NEEDED: Information Request: NDA 206317: FDA Proposed Carton Labeling for Triferic: Due January 5th
Attachments: Carton Container_Pouch with CMC proposed comments_121214.doc

Importance: High

Dear Dr. Pratt,

Please reference NDA 206317 for Triferic®, submitted March 24, 2014. We would like to request a prompt response to the following Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Information Request:

Please see attached FDA proposed revisions for Triferic's carton container, pouch and vial labels.

Please respond to this Information Request to me by email by **10:00 AM ET, Monday January 5, 2015**. You will need to also officially submit the information to your NDA.
Please confirm receipt of this message.

Kind regards,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
12/18/2014

Chi, Amy H

From: Chi, Amy H
Sent: Friday, December 12, 2014 6:59 AM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: NDA 206317 (Triferic) - FDA Proposed PI - Due December 19, 2014
Attachments: NDA 206317_Triferic_draft-labeling-text-word_sent to Rockwell_12.12.14.doc

Importance: High

Dear Dr. Pratt,

Please see attached revised draft of the PI for NDA 206317.

Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)

After you have made the changes, please send me the revised PI in tracked change before you make your official submission electronically.

Please provide a revised PI to me by close of business on **Friday, December 19, 2014**.

The review team is in the process of completing their review of the revised carton, pouch and ampule label. Once the review is completed, I will send the Division's comments to you. Also, the Division is finalizing Rockwell's PREA PMRs and will be sent to you for review.

Please contact me if you have any questions,

Kind regards,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
12/12/2014

PeRC PREA Subcommittee Meeting Minutes
November 12, 2014

PeRC Members Attending:
Wiley Chambers
George Greeley
Kevin Krudys
Lily Mulugeta
Freda Cooner
Dianne Murphy
Kristiana Brugger
Rachel Wittten
Greg Reaman
Hari Cheryl Sachs
Michelle Roth-Cline
Shrikant Pagay
Peter Starke

PREA

10:40	NDA	206317	Triferic (ferric pyrophosphate) Partial Waiver/Deferral/Plan *Agreed iPSP*	Iron replacement product for the treatment of iron loss and maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease.

Non Responsive

Triferic (ferric pyrophosphate) Partial Waiver/Deferral/Plan (Agreed iPSP)

- Proposed Indication: Iron replacement product for the treatment of iron loss and maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease.
- PeRC members were not in complete agreement with the dates provided for the PK study listed in the template.
- This application triggered PREA as a new: indication, dosage form, dosing regimen, route of administration.
- The PDUFA goal date is January 25, 2015
- *PeRC Recommendations*:
    - The PeRC agreed with the deferral in patients ages birth to less than 17 years because the product is ready for approval in adults.
    - The PeRC recommends that the Division encourage the sponsor to advance the timelines for the PK study.

Non Responsive

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/s/

GEORGE E GREELEY
12/05/2014

Chi, Amy H

bject: FW: RE: Facility Review in Panorama: Triferic, NDA 206317

From: Li, Zhong
Sent: Tuesday, December 02, 2014 8:20 AM
To: Chi, Amy H
Subject: RE: RE: Facility Review in Panorama: Triferic, NDA 206317

Amy,

Here is the old format of the EES report:

Application	NDA 206317/000
Sponsor	ROCKWELL MEDICAL
Status	PN
FEI	(b) (4) 3002808845
CFN	9615002
Establishment	HOLOPACK VERPACKUNGSTECHNIK GMBH (WORK 1)
Address	(b) (4)
Country	DEU
Profile	SLQ
Stage	FINISHED DOSAGE
Process	(b) (4) ,MANUFACTURER (b) (4) (b) (4)
Compliance Status	AC
Last EI Date	2/12/2014
OAI Alert Status	**NONE**
EER Re-eval Date	(b) (4)
Overall Recommendation	Acceptable
Decision Date	12/1/2014
Overall Re-eval Date	2/12/2016

Chi, Amy H

From: Chi, Amy H
Sent: Sunday, November 02, 2014 3:25 PM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: RESPONSE REQUIRED: Statistical Information Request: NDA 206317: Triferic (soluble ferric pyrophosphate) due November 3rd

Importance: High

Dear Dr. Pratt,

Please reference NDA 206317 for Triferic, submitted March 24, 2014. We would like to request a prompt response to the following Statistical Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Information Request:

1. Please provide the date of un-blinding for the NIH study.
2. Please confirm the finalized SAP date for the NIH study, **23Jan2013**. If it is not the date indicated, please provide the correct date.

Please respond to this Information Request to me by email by **COB Monday, November 3, 2014**. You will need to also officially submit the information to your NDA.

Please confirm receipt of this message.

Kind regards,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
11/02/2014

Chi, Amy H

From: Chi, Amy H
Sent: Tuesday, October 28, 2014 8:02 AM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: RESPONSE REQUIRED: Clinical Information Request: NDA 206317: Triferic (soluble ferric pyrophosphate) due today, October 29th

Importance: High

Dear Dr. Pratt,

Please reference NDA 206317 for Triferic, submitted March 24, 2014. We would like to request a prompt response to the following Clinical Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Information Request:

Please provide the following information:

1. How many patients were screened for entry into the Run-In period?
2. How many patients entered the run-in period?
3. How many qualified for entry into the randomized period?

Please respond to this Information Request to me by email by **3:00 PM Wednesday, October 29, 2014**. You will need to also officially submit the information to your NDA.

Please confirm receipt of this message.

Kind regards,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
10/28/2014

Note: The PeRC review of this product will likely occur *after* the Review Division checks this completed document into DARRTS. The PeRC's recommendation, which may differ from the information in this document, will be described in the PeRC meeting minutes. PeRC meeting minutes are linked in DARRTS to the INDs and applications discussed during each meeting.

Dear Review Division:

The attached template includes the necessary documentation to facilitate the *required* Pediatric Review Committee (PeRC) review of Waivers, Deferrals, Pediatric Plans, and Pediatric Assessments before product approval.

Complete the section(s) of this template that are relevant to your *current submission.*

Definitions:

Deferral *– A deferral is granted when a pediatric assessment is required but has not been completed at the time the New Drug Application (NDA), Biologics License Application (BLA), or supplemental NDA or BLA is ready for approval. On its own initiative or at the request of an applicant, FDA may defer the submission of some or all required pediatric studies until a specified date after approval of the drug or issuance of the license for a biological product if the Agency finds that the drug or biological product is ready for approval in adults before the pediatric studies are completed, the pediatric studies should be delayed until additional safety and effectiveness data have been collected, or there is another appropriate reason for deferral.*

Full Waiver *– On its own initiative or at the request of an applicant, FDA may waive the requirement for a pediatric assessment for all pediatric age groups if: (1) studies would be impossible or highly impracticable; (2) there is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups; or (3) the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, AND is not likely to be used in a substantial number of pediatric patients. If studies are being waived because there is evidence that the product would be ineffective or unsafe in all pediatric age groups, this information MUST be included in the pediatric use section of labeling.*

Partial Waiver *– FDA may waive the requirement for a pediatric assessment for a specific pediatric age group if any of the criteria for a full waiver are met for that age group or if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed. If a partial waiver is granted because a pediatric formulation cannot be developed, the partial waiver will only cover the pediatric groups requiring that formulation.*

Pediatric Assessment *– The pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required. It also includes data that are adequate to: (1) assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations; and (2) support dosing and administration for each pediatric subpopulation for which the data support a finding that the product is safe and effective.*

Pediatric Plan *– A pediatric plan is the applicant's statement of intent describing the planned or ongoing pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that they plan to conduct or are conducting (i.e., the pediatric studies that will comprise the pediatric assessment). If necessary, the plan should address the development of an age-appropriate formulation and must contain a timeline for the completion of studies. FDA recommends that the timeline should include the dates the applicant will: (1) submit the protocol; (2) complete the studies; and 3) submit the study reports.*

Pediatric Population/Patient- *21 CFR 201.57 defines pediatric population (s) and pediatric patient (s) as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.*

PREA Pediatric Record/Pediatric Page *– The pediatric record is completed for all NDAs, BLAs, or supplemental NDAs or BLAs. This record indicates whether the application triggers the Pediatric Research Equity Act (PREA), and if so, indicates how pediatric studies will be or have been addressed for each pediatric age group. If the Agency is waiving or deferring any or all pediatric studies, the pediatric record also includes the reason(s) for the waiver and/or deferral. (Note that with the implementation of DARRTS, the Pediatric Record is replacing the Pediatric Page for NDAs. The Pediatric Page is still to be used for BLAs.) For NDAs, the information should be entered into DARRTS and then the form should be created and submitted along with other required PeRC materials. Divisions should complete the Pediatric Page for NDAs that do not trigger PREA and submit the Pediatric Page via email to CDER PMHS until further notice.*

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND

Please check all that apply: ☐ **Full Waiver** ☐ **Partial Waiver** ☐ **Pediatric Assessment** ☒ **Deferral/Pediatric Plan**

BLA/NDA#: NDA 206317

PRODUCT PROPRIETARY NAME: Triferic® **ESTABLISHED/GENERIC NAME: soluble ferric pyrophosphate**

APPLICANT/SPONSOR: Rockwell Medical, Inc.

PREVIOUSLY APPROVED INDICATION/S:
(1) ***N/A***_____
(2) _____
(3) _____
(4) _____

PROPOSED INDICATION/S:
(1) Iron replacement product for the treatment of iron loss and maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease.
(2) _____
(3) _____
(4) _____

BLA/NDA STAMP DATE: March 24, 2014

PDUFA GOAL DATE: January 24, 2015

SUPPLEMENT TYPE: N/A

SUPPLEMENT NUMBER: N/A

Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

NEW ☐ active ingredient(s) (includes new combination); ☐ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration? New manufacturer

This application is a new NDA.

Did the sponsor submit an Agreed iPSP? Yes ☒ No ☐

Did FDA confirm its agreement to the sponsor's Agreed iPSP? Yes ☒ No ☐

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes ☐ No ☒

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes ☐ No ☒

If Yes, PMR #_____ NDA #_____

Does the division agree that this is a complete response to the PMR? Yes ☐ No ☐

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.

WAIVER REQUEST

Please attach:

☐ ***Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.***

☐ ***Pediatric Record***

1. Pediatric age group(s) to be waived.

2. Reason(s) for waiving pediatric assessment requirements (***Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for <u>each</u> age group or indication. This section should reflect the Division's thinking.***)

   ☐ Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from the adult-related conditions on the next page.

   ☐ The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information MUST be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.

   ☐ The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **<u>and</u>** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

   ☐ Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted***. (This reason is for Partial Waivers Only)***

3. Provide justification for Waiver:

4. Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:

Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics
These conditions qualify for waiver because studies would be impossible or highly impractical.

- actinic keratosis
- adjunctive treatment of major depressive disorder
- age-related macular degeneration
- Alzheimer's disease
- amyloidosis
- amyotrophic lateral sclerosis
- androgenic alopecia
- atherosclerotic cardiovascular disease
- autosomal dominant polycystic kidney disease (ADPKD)
- benign monoclonal gammopathy
- benign prostatic hyperplasia
- cancer:
  - basal cell and squamous cell skin cancer
  - bladder
  - breast
  - cervical
  - colorectal
  - endometrial
  - esophageal
- cancer (continued):
  - follicular lymphoma
  - gastric
  - hairy cell leukemia
  - hepatocellular
  - indolent non-Hodgkin lymphoma
  - lung (small & non-small cell)
  - multiple myeloma
  - oropharynx (squamous cell)
  - ovarian (non-germ cell)
  - pancreatic
  - prostate
  - refractory advanced melanoma
  - renal cell
  - uterine
- chronic lymphocytic leukemia
- chronic obstructive pulmonary disease
- cryoglobulinemia
- diabetic peripheral neuropathy / macular edema

digestive disorders (gallstones)

dry eye syndrome (keratoconjunctivitis sicca)

erectile dysfunction

essential thrombocytosis

Huntington's chorea

infertility & reproductive technology

ischemic vascular diseases, such as angina, myocardial infarction, and ischemic stroke

memory loss

menopause and perimenopausal disorders

mesothelioma

myelodysplasia

myelofibrosis & myeloproliferative disorders

osteoarthritis

overactive bladder

Parkinson's disease

paroxysmal nocturnal hemoglobinuria

plasma cells and antibody production disorders

polycythemia vera

postmenopausal osteoporosis

prevention of stroke and systemic embolic events in atrial fibrillation

psoriatic arthritis

reduction of thrombotic cardiovascular events in patients with coronary artery disease

replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone

retinal vein occlusions

stress urinary incontinence

temporary improvement in the appearance of caudal lines

treatment of incompetent great saphenous veins and varicosities

type 2 diabetic nephropathy

vascular dementia/vascular cognitive disorder/impairment

DEFERRAL REQUEST

Please attach:

☒ ***Pediatric Record***

1. **Age groups included in the deferral request: Birth to less than 18 years of age**

2. **Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request:**

3. **Reason/s for requesting deferral of pediatric studies in pediatric patients with disease:** (***Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for <u>each</u> age group or indication. This section should reflect the Division's thinking.***)

   a. Adult studies are completed and ready for approval - Yes
   b. Additional safety or effectiveness data needed (**describe**): Yes. Needed studies are described in the iPSP.
   c. Other (**specify**)

4. **Provide projected date for the submission of the pediatric assessment (deferral date): June 2021**

5. **Did applicant provide certification of grounds for deferring assessments?** ☒ **Yes** ☐ **No**

6. **Did applicant provide evidence that studies will be done with due diligence and at the earliest possible time?** ☒ **Yes** ☐ **No**

SPONSOR'S PROPOSED PEDIATRIC PLAN

1. Has a pediatric plan been submitted to the Agency? ☒ Yes ☐ No
   The sponsor submitted an initial Pediatric Study Plan (PSP) on 4/7/14 (IND 51290). The Division provided comments and recommendations from DHP to the Sponsor on 6/23/2014, 7/7/2014, 9/16/2014, 10/2/2014 and 10/3/2014. The sponsor submitted a revised PSP (Agreed-Upon Initial PSP) to DHP on 10/20/2014).

2. Does the division agree with the sponsor's plan? ☒ Yes ☐ No

3. Did the sponsor submit a timeline for the completion of studies (must include at least dates for protocol submission, study completion and studies submitted)? ☒ Yes ☐ No

PK studies:

Estimated protocol submission date:	Not later than March 2015
Estimated study initiation date:	Not later than September 2015
Estimated final report submission date:	Not later than September 2017

Efficacy/safety studies

Estimated protocol submission date:	Not later than March 2018
Estimated study initiation date:	Not later than September 2018
Estimated final report submission date:	Not later than December 2020

Target date of application submission: Approximately June 2021

4. Has a Written Request been issued? ☐ Yes ☒ No (If yes and the WR matches the proposed pediatric plan, please attach a copy. It is not necessary to complete the remainder of this document)

5. Has a PPSR been submitted? ☐ Yes ☒ No (If yes, you may submit a draft WR and have PeRC review WR and deferral/plan at the same time.)

Please note that the remainder of this section should be completed based on what the Division is requiring regardless of what the sponsor is proposing.

DIVISION'S PROPOSED PK, SAFTEY, AND EFFICACY TRIAL

Please complete as much of the information below as possible. Please note that the portions of the document that are shaded are not required for early stage pediatric plans but are useful if available.

Types of Studies/Study Design:

Nonclinical Studies:

Clinical Studies:

Study 1: Title: Pharmacokinetics of SFP iron delivered via dialysate in pediatric patients with chronic kidney disease on hemodialysis

Study Design: (b) (4).

Study 2: (b) (4)

(b) (4)

Number of patients to be studied or power of study to be achieved:

Example:

Study 1: X subjects in each treatment arm and be powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% must be females and 25% must be less than 3 years.

Study 2: This study is powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters.

Entry criteria:

This section should list pertinent inclusion/exclusion criteria.

(b) (4)

Clinical endpoints:

Study 1:

(b) (4)

Study 2:

(b) (4)

(b) (4)

Timing of assessments:

Example :baseline, week 1, 4, and 6

Statistical information (statistical analyses of the data to be performed):
Example:

Study 1: (b) (4)

.

Study 2: (b) (4)

Division comments on product safety:
Are there any safety concerns currently being assessed? ☐ **Yes** ☒ **No**

Are there safety concerns that require us to review post-marketing safety data before fully designing the pediatric studies? ☐ **Yes** ☒ **No**

Will a DSMB be required? ☐ **Yes** ☒ **No**

Other comments:

Division comments on product efficacy:
In the adult studies, the drug achieved its primary efficacy endpoint.

Division comments on sponsor proposal to satisfy PREA:

Full protocols have not yet been received. Additional comments may be provided to the sponsor upon review of the final protocols.

PeRC ASSESSMENT TEMPLATE

Please attach:

- ☐ ***Proposed Labeling from the sponsor unless the Division plans to change. If changing the language, include the appropriate language at the end of this form.***
- ☐ ***Pediatric Record***

Date of PREA PMR:
Description of PREA PMR: ***(Description from the PMC database is acceptable)***

Was Plan Reviewed by PeRC? ☐ **Yes** ☐ **No** If yes, did sponsor follow plan?

If studies were submitted in response to the Written Request (WR), provide the annotated WR in lieu of completing the remainder of the Pediatric Assessment template.

Indication(s) that were studied:
This section should list the indication(s) exactly as written in the *protocols.*

Example:
DRUG for the treatment of the signs and symptoms of disease x.

Number of Centers _____

Number and Names of Countries _____

Drug information:

Examples in italics

- **Route of administration**: *Oral*

• ***Formulation:** *disintegrating tablet* • **Dosage:** *75 and 50 mg* • **Regimen:** *list frequency of dosage administration* **If the dosage form is powder for oral suspension; provide information on storage statement and concentration after reconstitution (e.g. with water, juice or apple sauce etc.)*
Types of Studies/ Study Design:
Age group and population in which study/ies was/were performed:
Number of patients studied or power of study achieved: *Example:* *Study 1: X patients in each treatment arm and was powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% were females and 25% were less than 3 years.* ***Study 2: powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters. The study included at least X evaluable patients. .***
Entry criteria: This section should list pertinent inclusion/exclusion criteria.
Clinical endpoints:

Statistical information (statistical analyses of the data performed): This section should list the statistical tests conducted. *Example:* *Study 1 - two-sided 95% confidence interval (CI) of treatment difference in improvement rates were within 25% of the control's response rate.* *Study 2: descriptive statistical methods for AUC, C max, Tmax, Cl/F and compared to adults.*
Timing of assessments: *Example:* *Baseline, week 2, week, 6, and end of treatment*
Division comments and conclusions (Summary of Safety and Efficacy)

Provide language Review Division is proposing for the appropriate sections of the label if different from sponsor-proposed language.

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/s/

AMY H CHI
10/27/2014

Chi, Amy H

From: Chi, Amy H
Sent: Thursday, October 23, 2014 1:28 PM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: RESPONSE REQUIRED: Information Request: NDA 206317: Triferic (soluble ferric pyrophosphate) due October 29th

Importance: High

Dear Dr. Pratt,

Please reference NDA 206317 for Triferic, submitted March 24, 2014. We would like to request a prompt response to the following Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Information Request:

We are concerned that the dosing instruction you have proposed in the draft label for Triferic, namely, (b) (4) [redacted] 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 respond to this Information Request to me by email by **3:00 PM Wednesday, October 29, 2014**. You will need to also officially submit the information to your NDA.

Please confirm receipt of this message.

Kind regards,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
10/23/2014

Chi, Amy H

From: Chi, Amy H
Sent: Wednesday, October 22, 2014 11:43 AM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: RESPONSE REQUIRED: Clinical Information Request: NDA 206317: Triferic (soluble ferric pyrophosphate) due today, October 22nd

Importance: High

Dear Dr. Pratt,

Please reference NDA 206317 for Triferic, submitted March 24, 2014. We would like to request a prompt response to the following Clinical Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Information Request:

Please provide the following Tables as shown in Study NIH-FP-01 report for ITT population (n=108, SFP 54 and Placebo 54):

Table 7. Demographics
Table 8. Baseline Renal History
Table 9. Baseline Iron and Selected Chemistry and Hematology Parameters

Please respond to this Information Request to me by email by **COB today, October 22, 2014**. You will need to also officially submit the information to your NDA.

Please confirm receipt of this message.

Kind regards,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
10/22/2014

Chi, Amy H

From: Chi, Amy H
Sent: Tuesday, October 14, 2014 5:26 PM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: RESPONSE REQUIRED: Clinical Information Request: NDA 206317: Triferic (soluble ferric pyrophosphate) due October 16th

Importance: High

Dear Dr. Pratt,

Please reference NDA 206317 for Triferic, submitted March 24, 2014. We would like to request a prompt response to the following Clinical Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Information Request:

1. The datasets for pooled SFP-4 and SFP-5 safety analysis should be in xpt format (provide ASAP).
2. In subgroup analysis, patients who used cellulose triacetate dialyzer membrane showed no different from placebo in change in Hgb from baseline. Provide possible explanation and effect of dialyzer membrane on Triferic entering the blood. Provide information on different type of dialyzer membrane used in clinical practice.
3. There was small difference in death rate between the Triferic and placebo groups in Phase 3 trials. Provide possible explanation and additional analysis in 12 deaths in SFP-treated group for laboratory abnormalities in hematology (including hemoglobin), iron parameters, and chemistry tests (including electrolytes) during the trial.

Please respond to this Information Request to me by email by **2:00 PM Thursday, October 16, 2014**. You will need to also officially submit the information to your NDA.

Please confirm receipt of this message.

Kind regards,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
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(240) 402-0992 (phone)

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/s/

AMY H CHI
10/14/2014

Chi, Amy H

From: Chi, Amy H
Sent: Friday, October 10, 2014 9:40 AM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: RESPONSE REQUIRED: Clinical Information Request: NDA 206317: Triferic (soluble ferric pyrophosphate) due today, October 10th

Importance: High

Dear Dr. Pratt,

Please reference NDA 206317 for Triferic, submitted March 24, 2014. We would like to request a prompt response to the following Clinical Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Information Request:

1. There is a discrepancy in number of IDH and procedure hypotension in the SFP group (62 and 63, respectively) between the following two tables. Clarify and provide correct tables.

    - Table 8.28 Symptoms and Interventions Associated with Treatment-Emergent Adverse Events of Intra-Dialytic Hypotension SFP-4-RC and SFP-5-RC – Safety Population FDA Clinical Information Request - 16Sep2014
    - Table 8.17 Treatment-Emergent Adverse Events by Preferred Term SFP-4-RC and SFP-5-RC – Safety Population FDA Clinical Information Request - 16Sep2014

2. Provide location for datasets for pooled SFP-4 and SFP-5 safety analysis

Please respond to this Information Request to me by email by **3:00 PM Today, October 10, 2014**. You will need to also officially submit the information to your NDA.

Please confirm receipt of this message.

Kind regards,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
10/10/2014

Chi, Amy H

From: Chi, Amy H
Sent: Friday, October 10, 2014 5:58 AM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: RESPONSE REQUIRED: Statistical Information Request: NDA 206317: Triferic (soluble ferric pyrophosphate) due October 14th

Importance: High

Dear Dr. Pratt,

Please reference NDA 206317 for Triferic, submitted March 24, 2014. We would like to request a prompt response to the following Statistical Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Information Request:

1. For SFP-4-RC and SFP-5-RC, Please sent the following tables using the ITT population

Table 17. Iron Parameters - Pre- and Post-dialysis, Stage 2: MITT Population
Table 18. Change and Percentage Change from Baseline in CHr, Ferritin and the Pre-dialysis Serum Iron Panel, LOCF Analysis, Stage 2, MITT Population

2. For NIH-fp-01 study, Please sent the following tables and figure using the ITT population

Table 11. Percent Change from Baseline Prescribed ESA Dose: MITT Population
Table 12. Percent Change from Baseline Actual ESA Dose: MITT Population
Figure 1. Percent Change from Baseline in Prescribed ESA Dose By Study Week: MITT Population

Please respond to this Information Request to me by email by **12 noon Tuesday, October 14, 2014**. You will need to also officially submit the information to your NDA.

Please confirm receipt of this message.

Kind regards,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
10/10/2014

Chi, Amy H

From: Chi, Amy H
Sent: Wednesday, October 08, 2014 1:10 PM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: RESPONSE REQUIRED: Clinical Information Request: NDA 206317: Triferic (soluble ferric pyrophosphate) due October 9th

Importance: High

Dear Dr. Pratt,

Please reference NDA 206317 for Triferic, submitted March 24, 2014. We would like to request a prompt response to the following Clinical Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Information Request:

1. Provide the following incidence rate of laboratory abnormalities in Pooled SFP-4 and SFP-5 Studies and in ALL23 grouping (120-day safety update dataset) as separate tables.

	SFP N=292 n(%)	Placebo N=296 n(%)
ALT >2 x ULN		
ALT >3 x ULN		
AST >2 x ULN		
AST >3 x ULN		
Total bilirubin >2 x ULN		

Please respond to this Information Request to me by email by **3:00 PM Thursday, October 9, 2014**. You will need to also officially submit the information to your NDA.

Please confirm receipt of this message.

Kind regards,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
10/08/2014

Chi, Amy H

From: Chi, Amy H
Sent: Tuesday, October 07, 2014 10:30 AM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: RE: RESPONSE NEEDED: Information Request: NDA 206317: Triferic Carton Labeling: Response Due: October 24th

Importance: High

Dear Dr. Pratt,

Please reference NDA 206317 for Triferic®, submitted March 24, 2014. We would like to request a prompt response to the following Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Information Request:

Please make the following recommended changes to the proposed carton, pouch and ampule label.

A. Carton Labeling:

1. Express the product strength of the product on the principal display panel in terms of total quantity per total volume followed by the concentration per milliliter (mL)2,3. For example,

27.2 mg Fe/5 mL
(5.44 mg Fe/mL)

2. Increase the established name to at least half of the size of the proprietary name, to increase prominence commensurate with the proprietary name and in accordance with 21 CFR 201.10(g)(2).

3. On the principal display panel under the For Dialysis Use Only statement. Add this statement, ”Must be diluted”.

4. Replace the word (b) (4) with ampule, for the consistent use of the word “ampule” in the label and labeling, to read, “40 ampules”.

B. Pouch Labeling:

1. See A1 - A3 above.

2. Add this statement, “Each ampule is a single-use container” following the cautionary statements, Protect from light. Store unopened ampules in the foil envelopes until the time of use, etc.

3. If space permits, in the ampule per pouch sentence, remove the (b) (4) symbol and revise this current sentence to read instead,” (b) (4) pouch contains five 5 mL ampules each.”

C. Ampule Label:

1. Add the established name to the ampule per 21 CFR 201.10(i).

Please respond to this Information Request to me by email by 1:00 PM ET, Friday October 24, 2014. You will need to also officially submit the information to your NDA.
Please confirm receipt of this message.

Kind regards,

Amy

Amy Chi,
MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
10/07/2014

Chi, Amy H

From: Chi, Amy H
Sent: Monday, October 06, 2014 9:07 AM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: RESPONSE REQUIRED: Clinical Information Request: NDA 206317: Triferic (soluble ferric pyrophosphate) due today, October 6

Importance: High

Dear Dr. Pratt,

Please reference NDA 206317 for Triferic, submitted March 24, 2014. We would like to request a prompt response to the following Clinical Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Information Request:

1. Submit results for nonfatal treatment emergent serious adverse events (not all TESAEs) in pooled SFP-4 and SFP-5 studies, including all nonfatal TESAEs and related nonfatal TESAEs in separate tables.
2. Submit results for nonfatal treatment emergent serious adverse events (not all TESAEs) in All23 study grouping (120 day safety-update dataset), including all nonfatal TESAEs and related nonfatal TESAEs in separate tables.

Please respond to this Information Request to me by email by **4:00 PM today, October 6, 2014**. You will need to also officially submit the information to your NDA.

Please confirm receipt of this message.

Kind regards,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
10/06/2014

Chi, Amy H

From: Chi, Amy H
Sent: Friday, October 03, 2014 3:16 PM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: RESPONSE REQUIRED: Clinical Information Request: NDA 206317: Triferic (soluble ferric pyrophosphate) due October 6

Importance: High

Dear Dr. Pratt,

Please reference NDA 206317 for Triferic, submitted March 24, 2014. We would like to request a prompt response to the following Clinical Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Information Request:

1. Provide information in the Table below based on submitted result on 10/2/14.

	SFP N=292 n (%)	Placebo N=296 n (%)
TSAT ≥50%	42/282 (14.9)	18/289 (6.2)
Confirmed by 2 consecutive values measured at any time within a 2-week period (per		
Study drug administration was withheld (per protocol)		
Continued study drug treatment		
Ferritin ≥1200 µg/L	4/282 (1.4)	9/289 (3.1)
Confirmed by 2 consecutive values measured at any time		
Study drug administration was withheld (per protocol)		
Continued study drug treatment		

2. Provide the overall TEAEs as table shown below.

	SFP		Placebo	
	TSAT>=50% N=42 n(%)	TSAT<50% N=240 n(%)	TSAT>=50% N=18 n(%)	TSAT<50% N=271 n(%)
TEAEs				
TESAEs				
Deaths				

AEs leading to discontinuation				

3. Provide datasets for all pooled SFP-4 and SFP-5 analysis submitted on 10/2/14.

4. Clarify if only one ampoule was used at each HD session per patient in the Phase 3 trials. Otherwise provide the numbers in table below. Explain in detail how the final concentration of 110µg/L was calculated and provide the formula for the calculation.

	SFP-4	SFP-5
Triferic ampoules (5mL) used		
1		
2		
3		
Duration of dialysis session (hours)		
2		
3		
4		
Total volume of dialysate		

5. Provide summary and tables for clinical laboratory evaluation, including liver function tests, and ECG abnormalities based on the pooled SFP-4 and SFP-5 dataset. Provide related datasets also.

Please respond to this Information Request to me by email by **3:00 PM ET, Monday October 6, 2014**. You will need to also officially submit the information to your NDA.

Please confirm receipt of this message.

Kind regards,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP

(240) 402-0992 (phone)

APPEARS THIS WAY ON ORIGINAL

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/s/

AMY H CHI
10/03/2014

Chi, Amy H

From: Chi, Amy H
Sent: Tuesday, September 30, 2014 2:04 PM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: RESPONSE REQUIRED: Clinical Information Request: NDA 206317: Triferic (soluble ferric pyrophosphate) due October 2nd

Importance: High

Dear Dr. Pratt,

Please reference NDA 206317 for Triferic, submitted March 24, 2014. We would like to request a prompt response to the following Clinical Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Information Request:

1. For Tables submitted on 9/24/14, it is noted that the number of TEAEs, TESAEs, and others are slightly different from the combined numbers based on SFP-4 and SFP-5 study reports as shown below: e.g., TEAEs

   Pooled studies: (b) (4) TEAEs in SFP group
   SFP-4 report: (b) (4) TEAEs in SFP group
   SFP-5 report: (b) (4) TEAEs in SFP group

   Please check your program and resubmit all Tables for pooled SFP-4 and SFP-5 analysis if any changes are made.

2. Provide incidence rate for parameters in the following table for pooled SFP-4 and SFP-5 during randomized phase:

	SFP N=292 n(%)	Placebo N=296 n(%)
TSAT≥50%		
Ferritin ≥1200 ng/L		
Hgb ≥13 g/dL		
Hg ≥14 g/dL		

3. Provide incidence rate for parameters in the following table for pooled all SFP-treated patients (n=1411):

	SFP N=1411

	n(%)
TSAT≥50%	
Ferritin ≥1200 µg/L	
Hgb ≥13 g/dL	
Hg ≥14 g/dL	

4. Provide Table for TEAEs of composite cardiovascular event in pooled SFP-4 and SFP-5 studies. Include summary of the number of relevant events leading to study treatment discontinuation and number of SAEs.

5. Provide Table for TEAEs of HD vascular access/other thrombotic events in pooled SFP-4 and SFP-5 studies. Include summary of the number relevant events leading to study treatment discontinuation, number of SAEs, and outcomes.

6. Provide Table for TEAEs of systemic Infection. Include summary of the number of relevant events leading to study treatment discontinuation and number of SAEs.

7. Provide analysis of IV iron use (doses/month, any doses changes over time) in open-label extension phase based on all available studies (SFP-4-OL, SFP-5-OL, and SFP-6-OL).

8. TEAE preferred term (b) (4) is not acceptable. You need to identify each symptom under this term and re-analyze the data to provide a common TEAE Table in pooled SFP-4 and SFP-5 studies.

Please respond to this Information Request to me by email by **4:00 PM Thursday, October 2, 2014**. You will need to also officially submit the information to your NDA.

Please confirm receipt of this message.

Kind regards,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
09/30/2014

Chi, Amy H

From: Chi, Amy H
Sent: Tuesday, September 30, 2014 11:31 AM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: RESPONSE REQUIRED: Statistical Information Request: NDA 206317: Triferic (soluble ferric pyrophosphate) due October 7th

Importance: High

Dear Dr. Pratt,

Please reference NDA 206317 for Triferic, submitted March 24, 2014. We would like to request a prompt response to the following Statistical Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Information Request:

FDA has the following comment after reviewing the source code for MI. The dataset in MI procedure that contains the weekly missing Hgb values should be in horizontal rather than vertical format (one row should contains all the visits for each subject). For example, the missing Hgb value at week 10 should be imputed not only from trta, strat, and base, but also from the previous Hgb values at week 1-9.

Since there is small amount of missing data that is not monotone, FDA imputed the missing values in two steps. First, the MCMC method with monotone option was used to impute the intermediate missing values , then a monotone regression was used to imputed the rest. Due to large amount of missing at later weeks, FDA was only able to impute up to week 36 (month9) (i.e. up to week 36, it did not show any convergence problem). Please re-run your code based on the horizontal data format and nimpute=50 and submit the result in the ITT population.

Please respond to this Information Request to me by email by **12 noon Tuesday, October 7, 2014**. You will need to also officially submit the information to your NDA.

Please confirm receipt of this message.

Kind regards,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
09/30/2014

Chi, Amy H

From: Chi, Amy H
Sent: Friday, September 26, 2014 10:24 AM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: RESPONSE REQUIRED: Statistical Information Request: NDA 206317: Triferic (soluble ferric pyrophosphate) due October 3rd

Importance: High

Dear Dr. Pratt,

Please reference NDA 206317 for Triferic, submitted March 24, 2014. We would like to request a prompt response to the following Statistical Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Information Request:

1). For the PRIME (NIH) study, Please perform the statistical analyses on percent change from baseline in prescribed and actual ESA dosages using the MMRM model on ITT population with treatment as the factor and baseline Hgb as the covariate.

2). In the two pivotal studies (SFP-4-RC and SFP-5_RC), did stage 3 (open label phase) show Triferic reduce ESA dosage requirement? If so, please provide the results on ITT population.

Please respond to this Information Request to me by email by **3:00 PM (ET) Friday, October 3, 2014**. You will need to also officially submit the information to your NDA.

Please confirm receipt of this message.

Kind regards,

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

APPEARS THIS WAY ON ORIGINAL

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/s/

AMY H CHI
09/26/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206317

INFORMATION REQUEST

Rockwell Medical, Inc.
Attention: Raymond D Pratt, MD, FACP
Chief Medical Officer
30142 South Wixom Road
Wixom, MI 48393

Dear Dr. Pratt:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferric Pyrophosphate Solution, 5.44 mg Fe/mL.

We also refer to your original NDA submission.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a written response by September 29, 2014, in order to continue our evaluation of your NDA.

DRUG SUBSTANCE

1. Regarding the submitted structural elucidation information (NDA section 3.2.S.3.1) and the molecular structure information (NDA section 3.2.S.1.2):
   a. Provide a detailed drawing of the molecular structure of the proposed drug substance [redacted (b) (4)]. Provide the molecular formula and molecular weight range supported by this structure.
   b. Provide the changes in the structure of the complex when [redacted (b) (4)] drug substance is prepared into the solution of the drug product.
   c. Explain why the elemental analysis and molecular composition data does not correlate to the listed molecular structure; and why the proposed molecular formula does not correlate to the proposed molecular weight range.
   d. Provide data and information establishing whether [redacted (b) (4)] are present in the molecular structure of the complex. If yes, then specify how much of each ion is present and where they are present in the molecular structure of the complex.
   e. Provide a copy of the reports for the mass spectrometry, x-ray absorption near edge structure (XANES) spectroscopy, and extended x-ray absorption fine structure

(EXAFS) spectroscopy studies. Neither study results nor study reports were submitted in the NDA.

f. Describe the conditions under which [redacted] and how this affects the molecular structure and physical attributes of the drug substance.

2. Regarding the submitted characterization information:
   a. Specify whether bulk drug substance is [redacted] and describe the effect of residual [redacted] on the molecular structure and stability of the complex.
   b. Specify whether the complex shows pH dependent solubility in water and whether pH affects the stability of the complex in water.

3. Specify whether [redacted] ion, if present in the complex or drug product, will be transferred across the dialysis membrane and its affect to the safety of the patient.

4. Regarding the proposed manufacturing process for drug substance:
   a. [redacted]
   b.
   c.
   d.
   e.
   f. Describe how changes to the proposed manufacturing process or reagent ratios will affect the molecular structure and stability of soluble ferric pyrophosphate (SFP) complex.
   g. Specify the typical batch size for the commercial process and provide a list of the manufacturing equipment to be used with approximate capacities.

5. Regarding the proposed specifications for reagents and starting materials:
   a. Either add a limit for [redacted] to the specifications for [redacted] sulfate, [redacted] citrate and [redacted] pyrophosphate, or describe how the proposed specification addresses this impurity.
   b. For the specification for [redacted], establish acceptance criteria for residual metals and for heavy metals.
   c. For the specification for [redacted] citrate, establish acceptance criteria for heavy metals, residual [redacted], [redacted] content and alkalinity.
   d. Specify the grade of [redacted] used in the manufacturing process. If a [redacted] is added, then specify the [redacted] and the amount present.

6. Regarding the proposed drug substance release specification:
   a. Add a criterion for [redacted] content in the [redacted] associated with [redacted] drug substance. This is potential toxin in the drug product.
   b. Add an identity test for [redacted] using a method that is selective for these ions.

c. Report residual [(b) (4)] as "ppm" instead of [(b) (4)].
d. Justify the need for a limit of [(b) (4)] ppm residual [(b) (4)] when the levels observed in the phase 3 clinical and registration lots have typically been in the range of [(b) (4)] ppm.

7. Provide copies of the drug substance method validation study reports; only the summaries were submitted. The method validation study for Iron Content by ICP-OES should establish whether the method is selective for ferric and [(b) (4)] ions, and the recovery study should address the proposed range of [(b) (4)]% iron.

8. Regarding the submitted drug substance batch analysis data:
   a. Describe the changes to the manufacturing process and analytical methods which were implemented after the NDA registration lots were manufactured in 2008. Also, describe the effect these changes could have on the quality and stability of the proposed drug substance and proposed drug product.
   b. Provide the results of testing for [(b) (4)] on the NDA registration lots of drug substance.

9. Regarding the submitted drug substance stability information:
   a. Provide the results for content of [(b) (4)] in the samples from the forced degradation and photostability studies.
   b. Provide the results from [(b) (4)] testing on the samples from the forced degradation and dry heat studies.
   c. Explain the significant change in appearance [(b) (4)]) and in [(b) (4)] values observed in the photostability study samples. Specify what was lost, what was gained, and what changed.

DRUG PRODUCT

10. Regarding the submitted drug product in-use stability studies:
   a. Specify the expected range of compositions for the hemodialysis solution.
   b. Describe the effect of differences in the concentrations and compositions of bicarbonate concentrate [(b) (4)], and the quality of [(b) (4)] due to the multiple sources on the quality, stability and efficacy of the hemodialysis solution.
   c. Describe the possible differences in procedures for the preparation of the hemodialysis solution used at various administration sites on its quality, stability and efficacy.
   d. Specify whether the [(b) (4)] is the only acceptable procedure for the preparation of the hemodialysis solution.
   e. Specify whether any other diluents can be may be used in the preparation of the hemodialysis solution. If allowed, describe how the use of these other diluents will affect the quality, stability and efficacy of the hemodialysis solution.
   f. Describe how the in-use study test results address the formation of [(b) (4)] and why a test specific for [(b) (4)] is not included in the studies.
   g. Provide data and information which establishes that the ICP-OES method for iron determination used in the in-use studies is specific for [(b) (4)]

h. Provide data and information regarding the potential conversion of [redacted] in in the mixture of soluble ferric pyrophosphate concentrate with bicarbonate.

11. Regarding the proposed manufacture and control process for the drug product:
    a. [redacted]
    b.
    c.
    d.
    e.
    f. Describe the in-process test for container integrity; include the analytical method, acceptance criteria, and sample size and sampling frequency.
    g. Provide a list of the manufacturing equipment to be used for commercial production

12. Regarding the proposed drug product release specification:
    a. Provide an identity test which is specific for ferric ion. USP <191> is not an acceptable test for identity of ferric ion since it is not specific for ferric ion.
    b. Revise the specification to include a purity test for [redacted] and submit supporting analytical data on the registration batches. The method for iron assay is not specific for ferric ion, therefore is not acceptable to establish the assay and purity.
    c. Describe how the sample size and sampling frequency for the in-process control for fill weight/volume are adequate to address the requirement for unit dose uniformity as specified in USP <905>.
    d. Provide a justification for the criteria for anion content based on safety and efficacy of the hemodialysis solution, and quality and stability of the soluble ferric pyrophosphate concentrate.

13. Regarding the container/closure system for the drug product:
    a. Identify the contract lab which will perform testing on packaging components.
    b. Specify how often or when you will re-analyze the LDPE [redacted]
    c. Provide a detailed description (including material of composition and thickness of each [redacted]) and acceptance specification for the overpouch [redacted]
    d. Specify the supplier of the overpouch [redacted] and provide a copy of a certificate of analysis or certificate compliance from that supplier for the proposed [redacted]. Also, provide the results of acceptance testing on the lot(s) used in the manufacture of the NDA registration batches.

14. Regarding the submitted drug product stability information:
    a. Specify the acceptance criterion for [redacted] loss.
    b. Provide data on [redacted] in the samples placed on stability. [redacted]

MICROBIOLOGY

15. Specify any in-process control hold times for [redacted] (b) (4) and provide validation data demonstrating microbiological control for the proposed hold times.

16. Provide the integrity test acceptance criteria for the [redacted] (b) (4) used for Triferic [redacted] (b) (4) If a product-specific integrity test acceptance criteria was established, please provide the supporting data and calculations for the product-specific [redacted] (b) (4) integrity test value.

17. Provide s [redacted] (b) (4) process validation reports for [redacted] (b) (4) of the [redacted] (b) (4) machine(s) and associated equipment (e.g. [redacted] (b) (4), etc.), as well any [redacted] (b) (4) used for drug product manufacturing.

18. Identify the [redacted] (b) (4) for Triferic manufacturing, and provide current media fill data for each [redacted] (b) (4) identified.

If you have any questions, please contact Teicher Agosto, Regulatory Project Manager, at (240) 402-3777.

Sincerely,

{See appended electronic signature page}

Ali H. Al Hakim, PhD
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

ALI H AL HAKIM
09/18/2014

Chi, Amy H

From: Chi, Amy H
Sent: Tuesday, September 16, 2014 1:53 PM
To: Ray Pratt (rpratt@rockwellmed.com)
Cc: Carrie Guss (cguss@rockwellmed.com)
Subject: RESPONSE REQUIRED: Clinical Information Request: NDA 206317: Triferic (soluble ferric pyrophosphate) due September 24th

Importance: High

Dear Dr. Pratt,

Please reference NDA 206317 for Triferic, submitted March 24, 2014. We would like to request a prompt response to the following Clinical Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Information Request:

Provide the following safety information for Pooled Studies of SFP-4 and SFP-5 only (without NIH-FP-01) based on Tables in 2.7.4 Summary of Clinical Safety (SCS):

- Table 5. Exposure to Study Medication for SFP and Placebo-treated Subjects
- Table 7. Demographics
- Table 9. Overall Summary of TEAEs
- Table 11. Mortality by Treatment Group
- Table 12. Summary of TESAEs Occurring in ≥2% of SFP-treated Subjects by SOC and PT
- Table 14. TEAEs Leading to Study Discontinuation in ≥1 SFP-treated Subject by SOC and PT
- Table 16. Summary of TEAEs Reported in ≥2% of SFP-treated Subjects by SOC and PT
- Table 17. Summary of TEAEs Reported in ≥3% of SFP-treated Subjects by PT and Decreasing SFP Frequency
- Table 20. TEAEs by Duration of Exposure, SOC and PT
- Table 22. Most Common TEAEs by PT and Gender
- Table 23. Most Common TEAEs by PT and Age Group
- Table 24. Most Common TEAEs by PT and Race
- Table 25. Overall Summary of TEAEs of Special Interest in SFP and Placebo-treated Subjects
- Table 27. Summary of Incidence of Treatment-emergent IDH
- Table 28. Symptoms and Interventions Associated with TEAEs of IDH

Please respond to this Information Request to me by email by **3:00 PM ET, Wednesday, September 24, 2014**. You will need to also officially submit the information to your NDA.

Please confirm receipt of this message.

Kind regards,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
09/16/2014

Chi, Amy H

From: Chi, Amy H
Sent: Thursday, August 21, 2014 1:36 PM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: RESPONSE NEEDED: Clinical Information Request: NDA 206317 Triferic (soluble ferric pyrophosphate): Response Date: August 22

Importance: High

Dear Dr. Pratt,

Please reference NDA 206317 for Triferic, submitted March 24, 2014. We would like to request a prompt response to the following Statistical Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Clinical Information Request:

Please submit the patient narrative and CRF for one case of suspected hypersensitivity reactions in the placebo group.

Please respond to this Information Request by email by **2:00 PM on Friday, August 22, 2014.** Please also officially submit the document to your NDA. Please confirm receipt of this message.

Thank you,
Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
08/21/2014

Chi, Amy H

From: Chi, Amy H
Sent: Friday, August 15, 2014 2:26 PM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: RE: RESPONSE NEEDED: Clinical Information Request: NDA 206317 Triferic (soluble ferric pyrophosphate): Response Date: August 19

Importance: High

Dear Dr. Pratt,

Please reference NDA 206317 for Triferic, submitted March 24, 2014. We would like to request a prompt response to the following Clinical Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Clinical Information Request:

1. Provide patient narratives and case report forms for all 9 patients who had suspected hypersensitivity reactions among 1411 subjects in the ALL23 study grouping.
2. Provide summary information for all 44 deaths in SFP-treated patients as shown below.

Study name	Age/gender	Treatment duration (days on study)	Time to event leading to death since the last SFP dose	Time to death since the last SFP dose	Possible cause of death	Underlying conditions	Causality assessment

Please respond to this Information Request by email by **3:00 PM on Tuesday, August 19, 2014.** Please also officially submit the document to your NDA. Please confirm receipt of this message.

Kind regards,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
08/15/2014

Chi, Amy H

From: Chi, Amy H
Sent: Wednesday, August 13, 2014 3:12 PM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: RE: RESPONSES NEEDED: Statistical Information Request: NDA 206317 Triferic (soluble ferric pyrophosphate): Response Date: August 18

Importance: High

Dear Dr. Pratt,

Please reference NDA 206317 for Triferic, submitted March 24, 2014. We would like to request a prompt response to the following Statistical Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Statistical Information Request:

Please submit your SAS code for Multiple Imputation Analyses performed on the primary endpoint (Change from Baseline Hgb at EoT).

Please respond to this Information Request by email by **2:00 PM on Monday, August 18, 2014.** Please also officially submit the document to your NDA. Please confirm receipt of this message.

Thank you,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
08/13/2014

Chi, Amy H

From: Chi, Amy H
Sent: Wednesday, August 13, 2014 1:26 PM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: RE: RESPONSES NEEDED: Statistical Information Request: NDA 206317 Triferic (soluble ferric pyrophosphate): Response Date: August 18

Importance: High

Dear Dr. Pratt,

Please reference NDA 206317 for Triferic, submitted March 24, 2014. We would like to request a prompt response to the following Statistical Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Statistical Information Request:

Please provide a SAS dataset that contains treatment failure information during the randomized trial for SFP4 and SFP5. In the dataset, please contain the following for each subject: unique identifier, MITTFL, treatment group, indictor variables (Yes/No) for whether the subject ever: received blood transfusion, hgb < 9, ferritin <100, early withdraw the study, and early withdraw due to protocol mandated change.

Please respond to this Information Request by email by **2:00 PM on Monday, August 18, 2014.** Please also officially submit the document to your NDA. Please confirm receipt of this message.

Thank you,
Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
08/13/2014

Memorandum of Meeting Minutes

Application: NDA 206317
Sponsor: Rockwell Medical, Inc.
Meeting Type: FDA initiated Industry TCON
Date/Time: August 11, 2014; 2:15-2:40PM
Location: TCON; Bldg. 21; 1537

FDA Participants:

Ali Al Hakim, PhD, Branch Chief, ONDQA
Janice Brown, MS, CMC Lead, ONDQA
William Adams, PhD, CMC Reviewer, ONDQA
David Pudwill, Biomedical Engineer, CDRH
Neal Sweeny, PhD, Microbiology Reviewer, OPS
Jewell Martin, MA, MBA, PMP, Regulatory Health Project Manager

Rockwell Medical Participants:

Raymond D Pratt, MD, Chief medical Officer
Rob Chioini, CEO
Ajay Gupta, MD, Chief Scientific Officer
Ramesh Shukla, Ph.D., Head CMC
Margaret Studzinska, CMC leader
Carrie Guss, RDN, Head Clinical Operations
(b) (4)., CMC Consultant
(b) (4), Regulatory Consultant

Purpose of meeting:

The Agency requested references or submission of data to support in use labeling of the drug.

Meeting Notes:

Sponsor will provide the following CMC data to support NDA Submission:

1. A detailed description to support how the product is prepared in Section 2 - Dosage and Administration of label.

2. A In Use Stability report of the product and bicarbonate solution to support 24 hour storage time.

3. A report that indicates the stability of bicarbonate iron solution once mixed with acid and water in the dialysis machine.

4. Impurity analysis for active and excipients along with batch data to support the lack of testing for (b) (4) and excipient degradation.

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/s/

JEWELL D MARTIN
08/12/2014

Chi, Amy H

From: Chi, Amy H
Sent: Thursday, August 07, 2014 2:00 PM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: RESPONSE REQUIRED: Clin/Stats Information Request: NDA 206317: Triferic (soluble ferric pyrophosphate) - Response due Aug 14th

Importance: High

Dear Dr. Pratt,

Please reference NDA 206317 for Triferic, submitted March 24, 2014. We would like to request a prompt response to the following Clinical/Statistical Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Clinical/Statistical Information Request:

1. Please provide Tables for the protocol pre-specified secondary endpoints by treatment for both SFP-4 and SFP-5 studies for Stage 2:

- The incidence of "treatment failures," defined as decrease in Hgb to < 9 g/dL sustained for ≥ 2 consecutive weeks.
- The incidence of a decrease in Hgb of ≥ 1.0 g/dL from baseline sustained for ≥ 2 consecutive weeks.
- The incidence of decrease in ferritin to < 100 µg/L sustained for ≥ 2 consecutive weeks.
- The percent of patient maintaining Hgb concentration in the range of ≥ 9.5 to ≤ 11.5 g/dL for ≥80% of time on study.
- The percent of patients maintaining TSAT in the range of TSAT 20-50% for ≥80% of time on study.
- The percent of patients maintaining ferritin in the range of ferritin 200-800 µg/dL for ≥80% of time on study.

Please respond to this Information Request to me by email by **3:00 PM ET, Thursday, August 14, 2014**. You will need to also officially submit the information to your NDA.

Please confirm receipt of this message.

Kind regards,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
08/07/2014

Boehmer, Jessica

From:	Boehmer, Jessica
Sent:	Monday, August 04, 2014 4:26 PM
To:	rpratt@rockwellmed.com
Cc:	Chi, Amy H (Amy.Chi@fda.hhs.gov); Boehmer, Jessica
Subject:	RESPONSE REQUIRED: Clin/Stats Information Request: NDA 206317: Triferic (soluble ferric pyrophosphate) - Response due Aug 8th
Importance:	High

Dear Dr. Pratt,

Please reference NDA 206317 for Triferic, submitted March 24, 2014. We would like to request a prompt response to the following Clinical/Statistical Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Clinical/Statistical Information Request:

1. Please submit the following tables for **ITT population** (not MITT population) for **both studies (SFP-4 and SFP-5)** based on submitted tables in your study reports (**SFP-4-Stage-2-report-body-2 and SFP-4-Stage-2-report-body-2**)

   - Table 6. Demographics and Baseline Characteristics, Stage 2, ITT Population.
     - Include age group (<65 years. 65-74 years, and ≥75 years) in the table.
     - Include baseline hemoglobin value and iron parameters (TSAT, ferritin, TIBC, UIBC, serum iron, and CHr).
   - Table 7. Oral Iron Administration History, ITT Population
   - Table 8. IV Iron Administration History, Stage 2, ITT Population
   - Table 9. Summary of Hemodialysis Sessions, Stage 2, ITT Population
   - Table 10. Renal History, Stage 2: Safety Population
   - Table 11. Baseline ESA Prescription, Stage 2, ITT Population
   - Table 12. Study Drug Compliance, Stage 2, ITT Population
   - Table 16. Primary Efficacy Sensitivity Analysis No. 2 - MMRM - Hgb Mean Change from Baseline Using All Post-Baseline Values, Stage 2, ITT Population
   - Table 17. Iron Parameters - Pre- and Post-dialysis, Stage 2: ITT Population
   - Table 18. Change and Percentage Change from Baseline in CHr, Ferritin and the Pre-dialysis Serum Iron Panel, LOCF Analysis, Stage 2, ITT Population
   - Table 19. Variability of Hgb, Stage 2, ITT Population
   - Table 20. Percentage Change from Baseline ERI, LOCF Analysis, Stage 2, ITT Population
   - Table 21. Percentage Change from Baseline ERI/kg, LOCF Analysis, Stage 2, ITT Population

2. Please submit the following table for **safety population** (not MITT population) for both studies based on submitted tables in your study reports (SFP-4-Stage-2-report-body-2 and SFP-4-Stage-2-report-body-2)

   - Table 22. Study Drug Exposure, Stage 2, Safety Population

3. From Multiple Imputation that submitted on July 17, 2014, submit for ITT population

    - Table 16.1 and table 16.2 Primary Efficacy Sensitivity Analysis #2 – MMRM – Hemoglobin Mean Change from Baseline Using All Post-Baseline Values, Stage2, ITT Population – Multiple Imputation Sensitivity Analysis.

4. From submission on June 10, 2014, submit for ITT population

    - Table 14.2.2.1.1 Change from Baseline Hemoglobin by Time Point, LOCF Analysis, Stage 2, ITT Population

Please respond to this Information Request to Amy Chi and me by email by **2:00 PM ET, Friday, August 8, 2014**. You will need to also officially submit the information to your NDA.

Please confirm receipt of this message.

Kind regards,

Jessica

On behalf of Amy Chi, Regulatory Project Manager

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9849 (fax)

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/s/

JESSICA L BOEHMER
08/04/2014

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Thursday, July 31, 2014 5:47 PM
To: rpratt@rockwellmed.com
Cc: Chi, Amy H; Boehmer, Jessica
Subject: RESPONSE REQUIRED: Information Request: NDA 206317: Triferic (soluble ferric pyrophosphate) due Aug 4th

Importance: High

Dear Dr. Pratt,

Please reference NDA 206317 for Triferic, submitted March 24, 2014. We would like to request a prompt response to the following Statistical Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Information Request:

1. Currently, it appears there is only a pouch label and the picture of (b) (4) have been submitted. However, it appears the product should have a carton labeling to hold the pouches of Triferic. As a result, please submit the carton labeling if you intend to market it.
2. In terms of pouch label submitted, is this the pouch label that is intended to be marketed (e.g., (b) (4))?. If so, no additional action is needed at this time regarding pouch labeling. However, if a different pouch label is intended to be marketed, please submit it for our review.

Please respond to this Information Request to me by email by **4:00 PM ET, Monday, August 4, 2014**. You will need to also officially submit the information to your NDA.

Please confirm receipt of this message.

Kind regards,

Jessica

On behalf of Amy Chi, Regulatory Project Manager

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9849 (fax)

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/s/

JESSICA L BOEHMER
07/31/2014

Chi, Amy H

From: Chi, Amy H
Sent: Wednesday, July 02, 2014 5:39 PM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: RESPONSE NEEDED: Information Request: NDA 206317 Triferic (soluble ferric pyrophosphate): Response Date: July 7, 2014

Importance: High

Dear Dr. Pratt,

Please reference NDA 206317 for Triferic, submitted March 24, 2014. We would like to request a prompt response to the following Clinical Pharmacology Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Clinical Pharmacology Information Request:

Please provide the following:

1. The time-ordered dataset and the associated analysis files used in Study SFP-9 analysis. Domains related to demographics, calculated and measured iron-related as well as non-PK laboratory values should also be included.

2. The individual PK parameter estimates for the subjects in Study SFP-9 as SAS transport files.

Please refer to the following guidelines regarding general expectations of submitting pharmacometric data and models for guidance on submitting these data:
http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.

Please respond to this Information Request by email by **1:00 PM on Monday, July 7, 2014**. Please also officially submit the document to your NDA. Please confirm receipt of this message.

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
07/02/2014

Chi, Amy H

From: Chi, Amy H
Sent: Wednesday, July 02, 2014 3:12 PM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: RESPONSE NEEDED: Information Request: NDA 206317 Triferic (soluble ferric pyrophosphate): Response Date: July 14

Importance: High

Dear Dr. Pratt,

Please reference NDA 206317 for Triferic, submitted March 24, 2014. We would like to request a prompt response to the following Statistical Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Statistical Information Request:

Please clarify how you handle the rescue medication in your efficacy analyses. Also, please perform sensitivity analyses in consideration of rescue medication. For example, what are the impact to the magnitude of the effect size when rescue medications are handled in different ways? Please submit the appropriate analyses datasets (including variables for rescue medication use and start and stop dates for each patient).

Please respond to this Information Request by email by **1:00 PM on Monday, July 14, 2014.** Please also officially submit the document to your NDA. Please confirm receipt of this message.

Thank you,
Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
07/02/2014

Chi, Amy H

From: Chi, Amy H
Sent: Monday, June 30, 2014 2:33 PM
To: Ray Pratt (rpratt@rockwellmed.com)
Subject: RESPONSE NEEDED: Information Request: NDA 206317 Triferic (soluble ferric pyrophosphate): Response Date: July 8, 2014

Importance: High

Dear Dr. Pratt,

Please reference NDA 206317 for Triferic, submitted on March 24, 2014. We received Rockwell's response to the information request dated June 18, 2014. Please find below FDA's response with additional information request. We request a prompt response to the following Clinical Pharmacology Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Rockwell's response dated June 23, 2014

Q1:
How would the agency like the Hgb change rates expressed g/L/week or g/L/4 week interval? Given the mechanism of action of Triferic (SFP) we believe rates over 4 weeks are more appropriate, but we will do weekly changes if that is your preference.

We are planning to analyze the rate of change from baseline over each 8 week interval/patient/group and express a single value per patient for the average rate of change for the interval. The initial statistical analysis will look at the rates of change between each group at each interval to see if there are statistically significant differences in the change rates. Does the agency agree with this approach?

FDA's Response: Please provide clarification on the difference in definition between Hgb change rates in the first paragraph and the rate of change in Hgb from baseline in the second paragraph besides the length of interval (4 wks vs. 8 wks) and how they would be calculated. Given that Hgb samples were collected every 2 weeks, expressing the rates as g/L/2 weeks and g/L/4 weeks instead of weekly is okay.

The control 23 dataset (CONT23) contains data from two different studies: CRUISE, where ESA dose could not vary and no IV iron was allowed, and PRIME where patients could vary the dose of ESA and could also receive IV iron. We are planning to perform the analysis on the entire dataset without separating the studies. Does the agency agree?

FDA's Response: Please perform the analysis for each study separately. In addition, you could perform the analysis for the combined data, however, an appropriate weighting scheme for the two studies should be provided.

a. *If the effects are significantly different, use an appropriate, statistical method such as Mixed-Effect Model Repeated Measures (MMRM) model for #4 and #5*

For this question, we suggest that the MMRM model use all available Hgb values across all intervals. Does the agency agree with this approach.

Q4. The safety parameters to be investigated include those specified in the clinical studies as Adverse Events of special interest, including deaths, combined cardiovascular events, thrombotic events associated with dialysis access other than venous thrombosis, venous thrombosis (other thrombotic events), systemic serious infections and Intradialytic hypotension. Does the agency agree with this general categorization of AE?

FDA's Response: The proposed method did not address the issue of whether or not the rates of change in Hgb or iron level are different over time intervals. FDA requests that different rate of changes over time should be analyzed based on MMRM. If the rate of change in different intervals agrees with each other in terms of direction and magnitude (after appropriate hypothesis testing via MMRM), then they can be combined into one single value and compared between the treatment groups. If, however, the rate of changes are quite different, the statistical analysis based on MMRM should be used to reflect this difference.

Please respond to this Information Request by email by **2:00 PM on Tuesday, July 8, 2014**. Please also officially submit the document to your NDA. Please confirm receipt of this message.

Kind regards,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
06/30/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206317

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Rockwell Medical, Inc.
30142 South Wixom Road
Wixom, MI 48393

ATTENTION: James L. Hinson
Head of Regulatory Affairs

Dear Mr. Hinson:

Please refer to your New Drug Application (NDA) dated and received March 24, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferric Pyrophosphate Solution, 5.44 mg Fe/mL.

We also refer to your April 3, 2014, correspondence, received April 3, 2014, requesting review of your proposed proprietary name, Triferic.

We have completed our review of the proposed proprietary name, Triferic and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your April 3, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Kevin Wright, PharmD, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3621. For any other information regarding this application, contact Amy Chi, Regulatory Project Manager in the Office of New Drugs, at (240) 402-0992.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
06/26/2014

Chi, Amy H

From:	Chi, Amy H
Sent:	Wednesday, June 18, 2014 7:30 PM
To:	Ray Pratt (rpratt@rockwellmed.com)
Cc:	Garvey, Patricia
Subject:	RESPONSE NEEDED: Information Request: NDA 206317 Triferic (soluble ferric pyrophosphate): Response Date: July 9, 2014
Importance:	High

Dear Dr. Pratt,

Please reference NDA 206317 for Triferic, submitted March 24, 2014. We would like to request a prompt response to the following Clinical Pharmacology Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Clinical Pharmacology Information Request:

Please conduct the following analysis for the CONT23 dataset:

1. Calculate the rate of change in Hgb and serum iron for each patient.
    a. Calculate the rate of change in Hgb and serum iron for each one sixth treatment period (approximately 8 weeks)
    b. Perform hypothesis tests to see if these rates are significantly different from each other. If the effects are significantly different, use an appropriate, statistical method such as Mixed-Effect Model Repeated Measures (MMRM) model for #4 and #5
2. Calculate time for Hgb to increase ≥ 1 g/L
3. Calculate proportion of patients with an increase in Hgb ≥ 1 g/L
4. Evaluate the relationship between the aforementioned parameters and safety parameters including death.
5. Evaluate the relationship between baseline covariates and the aforementioned parameters listed in in 1, 2 and 3. The objective is to identify baseline factor(s) that are associated with the above mentioned safety parameters

Please provide the relevant datasets and programing code for these analyses.

Please respond to this Information Request by email by **1:00 PM on Wednesday, July 9, 2014**. Please also officially submit the document to your NDA. Please confirm receipt of this message.

Kind regards,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

APPEARS THIS WAY ON ORIGINAL

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/s/

AMY H CHI
06/23/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206317

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Rockwell Medical, Inc.
Attention: Robert L. Chioini
Chief Executive Officer and President
30142 S. Wixom Road
Wixom, MI 48393

Dear Mr. Chioini:

Please refer to your New Drug Application (NDA) dated March 24, 2014, received March 24, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Triferic™ (Soluble Ferric Pyrophosphate) Concentrate Solution, 5.44 mg Fe/mL.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is January 24, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by December 27, 2014.

During our filing review of your application, we identified the following potential review issues:

Clinical:

1. For the proposed indication for reduction of the ESA and (b) (4) requirements in CKD 5HD patients, the submitted NIH-FP-01 study was an exploratory Phase 2 study and the results may not be adequate to support the indication.

2. Provide detailed analysis (with dataset) for patients who withdrew from study due to "Protocol Mandated Changes in Anemia Management" for Studies RMTI-SFP-4 and RMTI-SFP-5. The analysis should be based on criteria defined in the protocol for ESA dose change (Hgb < 9.0 g/dL, Hg >12.0 g/dL) and for IV iron administration (serum ferritin < 100 µg/L).

3. Provide detailed analysis (with dataset) for patients who withdrew from study due to Non-protocol-mandated change in anemia management (ESA dose change, IV iron administration). The analysis should include detailed reasons for ESA dose change and for IV iron administration.

Chemistry, Manufacturing and Controls:

1. Provide information which addresses (b) (4) and (b) (4) in the drug substance and drug product at release and on storage.

2. Provide a limit for the safe level of (b) (4) as (b) (4) in drug substance and drug product. The limit should be justified based on patient exposure and route of administration.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

Chemistry, Manufacturing and Controls:

1. 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.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

1. Highlights (HL) must be in two-column format with ½ inch margins on all sides and between columns.

2. The length of HL must be one-half page or less.

3. A horizontal line must be inserted to separate the Highlights from the Table of Contents. Also, a horizontal line must be inserted to separate the TOC from the Full Prescribing Information (FPI).

4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column. The headings should be in UPPER CASE letters.

5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval.

6. In Highlights, delete the Recent Major Changes heading since it is not applicable to this application.

7. In Highlights, the patient counseling information statement should be revise to "See 17 for PATIENT COUNSELING INFORMATION" because there is not a patient labeling with this product.

8. The revision date at the end of HL will need to be revise to reflect the approval month and year when appropriate.

9. The TOC must be in a two-column format, all section headings must be **bolded**, and all subsection headings must be indented.

10. In the TOC and FPI, Section "8 Use in Specific Populations" change the subsection numbering for (b) (4).

11. In the TOC and FPI, the heading of subsection 13.1 and 13.2 must be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

12. In the FPI, the entire cross-reference must be in italics.

13. In the FPI, Section "4 Contraindications" must be added because it is a required section. If no Contraindications are known, this section must state "None."

14. In the FPI Section "6 ADVERSE REACTIONS", subsection (b) (4), delete subheading numbers (b) (4). The subheading titles may remain.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by June 23, 2014. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Amy Chi, Regulatory Project Manager, at (240) 402-0992.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Division Director
Division of Hematology Products
Division of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ANN T FARRELL
06/02/2014

Chi, Amy H

From: Chi, Amy H
Sent: Tuesday, May 27, 2014 9:56 AM
To: jhinson@rockwellmed.com
Subject: RESPONSE NEEDED: Information Request: NDA 206317 Triferic (soluble ferric pyrophosphate): Response Date: June 3rd

Dear Mr. Hinson,

Please reference NDA 206317 for Triferic, submitted March 24, 2014. We would like to request a prompt response to the following Statistical Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Statistical Information Request:

Please divide adlb.xpt into two separate files. One contains primary and key secondary endpoints and the other contains the rest.

Please respond to this Information Request by email by **1:00 PM on Tuesday, June 3, 2014**. Please also officially submit the document to your NDA. Please confirm receipt of this message.

Thank you,
Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
05/27/2014

Chi, Amy H

From: Chi, Amy H
Sent: Tuesday, May 27, 2014 9:54 AM
To: jhinson@rockwellmed.com
Subject: RESPONSE NEEDED: Information Request: NDA 206317 Triferic (soluble ferric pyrophosphate): Response Date: June 10th

Importance: High

Dear Mr. Hinson,

Please reference NDA 206317 for Triferic, submitted March 24, 2014. We would like to request a prompt response to the following Statistical Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Statistical Information Request:

1. Intent-to-Treat (ITT) should be used for all efficacy analysis. Please provide results for all the efficacy endpoints (primary and key secondary) using the ITT population.
2. For those patients who did not have any Hgb measurements during the last 1/6 of randomized treatment period or who did not have any post-baseline assessment, please clarify which imputation scheme has been used for the primary efficacy endpoint.
3. Please perform sensitivity analyses on missing data for the primary efficacy endpoint based on different imputation schemes. For example, based on multiple imputation, imputed with mean hgb value for patients who were in the same strata in each arm, worst case scenario, etc.
4. Please perform sensitivity analyses on missing data for the key secondary efficacy endpoints based on different imputation schemes. For example, based on multiple imputation, imputed with mean hgb value for patients who were in the same strata in each arm, worst case scenario, etc.
5. Please provide the data unblinding date for studies SFP-4, SFP-5 and NIH-FP-01 .

Please respond to this Information Request by email by **1:00 PM on Tuesday, June 10, 2014**. Please also officially submit the document to your NDA. Please confirm receipt of this message.

Thank you,
Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
05/27/2014

Chi, Amy H

From: Chi, Amy H
Sent: Thursday, May 15, 2014 11:41 AM
To: jhinson@rockwellmed.com
Subject: RESPONSE NEEDED: Information Request: NDA 206317: Triferic (soluble ferric pyrophosphate): Response Due: May 19th

Importance: High

Dear Mr. Hinson,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for soluble ferric pyrophosphate (Triferic).

We continue to review your NDA 206317 and request additional information.

Information Request:

Please provide the CRO contact name, phone number and email for (b) (4) where the data is located.

(b) (4)

Contact:
Phone:
E-mail:

Please respond to this Information Request by email by **1:00 PM on Monday, May 19, 2014.**

Please confirm receipt of this message.

Please let me know if you have any questions.

Kind regards,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
05/15/2014

Chi, Amy H

From: Chi, Amy H
Sent: Monday, April 28, 2014 1:35 PM
To: jhinson@rockwellmed.com
Subject: RESPONSE NEEDED: Information Request: NDA 206317: Triferic (soluble ferric pyrophosphate): Response Due: May 2, 2014

Importance: High

Dear Mr. Hinson,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for soluble ferric pyrophosphate (Triferic).

We continue to review your NDA 206317 and request additional information regarding Protocol RMTI-SFP-4 and RMTI-SFP-5 in PDF electronic format:

Information Request:

Provide study patient data listings, organized by clinical site number, to include the following elements below, for your adequate and well-controlled studies in PDF format:

A. Study Protocol RMTI-SPF-4 (Shayan Shirazin, M.D. Site 406 and Kant Tucker, MD Site 424)
B. Study Protocol RMTI-SPF-5 (Kailash Jindal, M.D. Site 508 [Canada] and Serge Cournoyer, MD Site 529 [Canada])

The study subject data listings should capture the following, as applicable:
(1) Subject discontinuations (If applicable per treatment group: site subject number, screening visit date, date of first dose/last dose, length of date of discontinuation, reason for discontinuation).
(2) Randomization listing
(3) Prior and concomitant medications (non-study medications): (If applicable per treatment group: site subject number, type (prior and/or concomitant meds), medication (preferred term), indication/reason taken, date started, date stopped.
(4) Prohibited medications (non-study medications): as above with concomitant medications
(5) Adverse events, (If applicable per treatment group: preferred term/investigator entry, detailed drug name, blinded-phase active dose, date start/stopped, severity/resolution, Serious Adverse Events (yes, no), death (yes/no)). Include laboratory or non-invasive tests of special interest, if applicable, performed for safety monitoring.
(6) Primary efficacy endpoint (If applicable per treatment group: site subject number, visit # and corresponding date in MM/DD/YY format (screening, baseline, week 1….etc).
(7) Protocol Deviations

Please respond to this Information Request by **1:00 PM on Friday, May 2, 2014.** Please send your response via an official response sent to NDA 206317.

Please confirm receipt of this message.

Please let me know if you have any questions.

Kind regards,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
10903 New Hamphire Ave, Building 22, Rm 2361
(240) 402-0992 (phone)

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/s/

AMY H CHI
04/28/2014

Chi, Amy H

From: Chi, Amy H
Sent: Wednesday, April 23, 2014 11:55 AM
To: jhinson@rockwellmed.com
Subject: RESPONSE NEEDED: Information Request: NDA 206317: Triferic (soluble ferric pyrophosphate): Response Due: April 25th

Importance: High

Dear Mr. Hinson,

Please reference new NDA 206317 for Triferic (soluble ferric pyrophosphate) submitted March 24, 2014. We would like to request a prompt response to the following Information Request.

Information Request:

Please provide the phone number, email and fax number for the following contact/sites:

1. Site: 406
   Shayan Shirazian MD
   Winthrop University Hospital
   200 Old Country Road
   Suite 135
   Mineola, NY 11501

2. Site: 424
   Kant Tucker MD
   424 Kidney Center of Northridge
   18546 Roscoe Blvd
   Suite 108
   Northridge, CA 91324

3. Site: 508
   Kailash Jindal, MD
   University of Alberta Hospital
   Edmonton
   T6G 2B7
   Canada
   WMC 5C2 (dialysis unit)

4. Site: 529
   Serge Cournoyer, MD
   Hospital Charles Lemoyne
   Research Center, Suite E-300
   Greenfield Park
   J4V 2H1
   Quebec, Canada

Please respond to this Information Request by email by **3:00 PM on Friday, April 25, 2014**.
Please confirm receipt of this message.

Please let me know if you have any questions.

Kind regards,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
04/23/2014

Chi, Amy H

From: Chi, Amy H
Sent: Friday, April 04, 2014 11:11 AM
To: jhinson@rockwellmed.com
Cc: Boehmer, Jessica; Carioti, Theresa
Subject: RESPONSE NEEDED: Information Request: NDA 206317: Triferic (soluble ferric pyrophosphate): Response Due: April 7, 2014

Dear Mr. Hinson,

Please reference new NDA 206317 for Triferic (soluble ferric pyrophosphate) submitted March 24, 2014. We would like to request a prompt response to the following Information Request.

Your NDA (206317) submission triggers the Pediatric Research Equity Act (PREA); therefore, an Agreed PSP (initial or amended) should have been in place before submission of the NDA. It is expected that the Sponsor submits an initial PSP [SD Pediatric Study Plan/Initial Pediatric Study Plan] to the IND or pre-IND within 60 days of an EOP2 meeting or prior to initiation of Phase 3 studies or 210 days prior to submission of a marketing application to allow the Agency to respond and provide comments.

Information Request:

Please officially submit your Pediatric Study Plan under your IND (52190) for review by the Agency.

Please respond to this Information Request by email by **3:00 PM on Monday, April 7, 2014**.
Please confirm receipt of this message.

Please let me know if you have any questions.

Kind regards,

Amy

Amy Chi, MSN
LCDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
04/04/2014

Chi, Amy H

From: Chi, Amy H
Sent: Monday, March 31, 2014 2:12 PM
To: 'jhinson@rockwellmed.com'
Cc: rchioini@rockwellmed.com
Subject: RESPONSE NEEDED: Information Request: NDA 206317: Triferic (soluble ferric pyrophosphate): Response Due: April 7, 2014

Importance: High

Dear Mr. Hinson,

Please reference new NDA 206317 for Triferic (soluble ferric pyrophosphate) submitted March 24, 2014. We would like to request a prompt response to the following Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting to the NDA.

Information Request:

Please submit a formal submission requesting a Proprietary Name Review for this new NDA.

Please respond to this Information Request by email by **3:00 PM on Monday, April 7, 2014**. Please also officially submit the document to your NDA. Please send your response to me.
Please confirm receipt of this message.

Kind regards,

Amy

Amy Chi, MSN
LCDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
03/31/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206317

NDA ACKNOWLEDGMENT

Rockwell Medical, Inc.
Attention: Robert L. Chioini
Chief Executive Officer and President
30142 S. Wixom Road
Wixom, Michigan 48393

Dear Mr. Chioini:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Triferic™ (Soluble Ferric Pyrophosphate)

Date of Application: March 24, 2014

Date of Receipt: March 24, 2014

Our Reference Number: NDA 206317

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 23, 2014 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.
If you have any questions, call me at (240) 402-0992.

Sincerely,

{See appended electronic signature page}

Amy Chi, MSN
Regulatory Project Manager
Division of Hematology Products
Division of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

AMY H CHI
03/31/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 51290

MEETING MINUTES

Rockwell Medical, Inc.
Attention: Mr. James Hinson
Head of Regulatory Affairs
Rockwell Medical, Inc.
30142 Wixom Road
Wixom, MI 48393

Dear Mr. James Hinson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for *Triferic* (Soluble Ferric Pyrophosphate).

We also refer to the teleconference between representatives of your firm and the FDA on November 26, 2013. The purpose of the meeting was to discuss CMC information to be included in the upcoming NDA submission.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Ali H. Al Hakim, PhD
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	CMC, Pre-NDA
Meeting Date and Time:	November 26, 2013; 11:00 AM – 12:00PM (EST)
Meeting Location:	TCON
Application Number:	IND 51290
Product Name:	*Triferic* (Soluble Ferric Pyrophosphate)
Indication:	Iron Replacement in Hemodialysis Patients/ (b) (4) Treatment of Iron Deficiency in Hemodialysis Patients
Sponsor/Applicant Name:	Rockwell Medical, Inc.
Meeting Chair:	Ali Al Hakim, Branch Chief, ONDQA
Meeting Recorder:	Jewell Martin, Regulatory Project Manager, ONDQA

FDA ATTENDEES
Ali Al Hakim, PhD, Branch Chief, ONDQA
Janice Brown, MS, CMC Lead, ONDQA
Debasis Ghosh, PhD, CMC Reviewer, ONDQA
Jewell Martin, MA, MBA, PMP, Regulatory Project Manager, ONDQA
Teicher Agosto, PharmD, Regulatory Project Manager, ONDQA
Vinayak Pawar, PhD, Microbiology Review, OPS
Theresa Carioti, MS, Regulatory Project Manager, DHP
Kathy Suh Robie, MD, Medical Officer, DHP

SPONSOR ATTENDEES
Rameshwar Shukla, PhD, Director CMC, Rockwell Medical
James Hinson, Head of Regulatory Affairs, Rockwell Medical
Ajay Gupta, MD, Chief Scientific Officer, Rockwell Medical
Raymond Pratt, MD, Chief Medical Officer, Rockwell Medical

Consultants (for Rockwell Medical)
(b) (4), CMC Consultant
(b) (4)

1.0 BACKGROUND

On October 9, 2013, the Agency received a TYPE B, CMC, Pre-NDA Meeting Request from Rockwell Medical Inc. The purpose of this meeting was to discuss CMC information to be included in the upcoming NDA submission. The sponsor submitted the meeting background package with the meeting request. A Meeting Granted letter was sent by the Agency on October 25, 2013. The Agency Preliminary Comments were sent on November 21, 2013. On November 22, 2013, after reviewing the comments the sponsor requested to change the meeting format from a face to face meeting to a teleconference. Additionally the sponsor stated that the Agency's comments to Questions 2,3,4,&5 were clear and required no further discussion. The sponsor stated that they would like to focus discussion to Question 1a & 1b. PowerPoint slides were submitted in order to facilitate discussion, see attached.

2. DISCUSSION

Question 1:
Question 1a: Does the Agency agree with the sponsor's designation of these materials as regulatory starting materials?

You have not provided adequate evidence to justify the structure of the proposed drug substance (Soluble Ferric Pyrophosphate or SFP); therefore, we are unable to make a determination of the adequacy of the starting material at this time.

In your NDA, provide supporting analytical data including X-ray crystallography (if available) to confirm the proposed (b) (4) structure and stoichiometry of Fe(III) complex (SFP).

If your data supports that SFP is the drug substanc (b) (4) can be designated as the starting materials, as proposed.

The proposed control strategy for the starting materials is acceptable. Please note that the proposed specifications of the compendial materials should be consistent with the compendial standards. For non-compendial materials, a justification for specifications should be provided in the NDA.

Please note that the adequacy of the information will be determined at the time of NDA review.

Question 1b: Does the Agency agree with the sponsor that the specifications and test methods adequately control the regulatory starting materials?

FDA Response to Question1b:

See response to Q1a. Submit the following information for SFP in your NDA:

For an active ingredient and non-compendial inactive ingredients, provide detailed information on the Chemistry Manufacturing and Controls or cross-reference it in an active Drug Master File (DMF) with a letter of authorization (LOA) form the DMF holder.

For compendial inactive ingredient, the specification and test method for compendial materials should be consistent with compendial standard.

Meeting Discussion:
1a. The Agency stated that the proposed starting materials appear acceptable. The sponsor agreed to provide a tabulated summary of the batch data for different vendors for each starting material along with the in-house testing results. The acceptability will be determined during the review of the NDA.

1b. The sponsor clarified that the starting materials will be tested according to the in-house specifications and the COA will be provided in the NDA.

Additional Comments:
The sponsor agreed to provide the molar ratios of the components of SFP values for x, y, and z (i.e., Iron, citrate, and pyrophosphate) in the NDA.

Question 2:
Does the Agency concur with the sponsor that the submission of this information in the NDA provides adequate support that the filling and packaging of SFP Concentrate using the (b) (4) process leads to a sterile and nonpyrogenic drug product for parenteral use?

FDA Response to Question 2:
From Product Quality Microbiology perspective, the outlined information in Module 3.2.P.3.5 pertaining to the (b) (4) and the (b) (4) appears to be in line with the submission requirements. However, the contents of the final submission and the acceptance of the microbiological results will be a review issue.

The sponsor is reminded to refer to the following guidance when submitting the NDA application: Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, Final 11/1994 (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072171.pdf) and MAPP 5040-1, for CTD format.

Sterilization validation information that will be submitted in the NDA application should include (and is not limited to) the following:

- (b) (4)

- (b) (4)
- **Environmental monitoring program (action levels and responses).**
- **Container-closure integrity studies for the primary container-closure system.**
- **Method suitability studies for the sterility and bacterial endotoxins tests for the finished product.**

Meeting Discussion:
No further discussion required.

Question 3:
Does the Agency agree with this approach?

FDA Response to Question 3:
Your proposal to provide the information on the commercial formulation or SFP concentrate appears reasonable. However, we recommend that you include relevant CMC information (e.g. specification, batch data, in-use stability) (b) (4) **in the product development section (Module 3.2.P.2.) in your NDA. Please note that the adequacy of the information will be determined at the time of NDA review.**

Meeting Discussion:
No further discussion required.

Question 4:
A. Does the agency concur with the sponsor that if no extractables of concern are identified in the ongoing (b) (4) study the information on the drug product container closure system will provide adequate support for NDA approval?
B. In case there are some extractables of concern identified in the ongoing study by (b) (4), the sponsor intends to develop and validate the appropriate analytical procedures to monitor these during post approval long-term stability studies at 25°C ± 2°C/60% RH ± 5% RH. Does the agency agree with this approach?

FDA Response to Question 4:
Your proposed plan to monitor leachables and extractables appears to be rational. Identify the chemical species of each extractable and determine whether it migrates into the dosage form. If any leachables are present, perform a toxicological evaluation and include the results in the NDA.

The risk associated with any leachable of concern is high. In case there are any leachables of concern identified in the ongoing study, the issue should be resolved before the NDA can be approved.

Please refer to the following guidance document: Guidance for Industry - Container

Closure Systems for Packaging Human Drugs and Biologics May 1999 (http://www.fda.gov/downloads/Drugs/Guidances/ucm070551.pdf)

Meeting Discussion:
No further discussion required.

Question 5:
Does the Agency agree that this labeling is appropriate?

FDA Response to Question 5:
It is premature to discuss the proposed labeling language at this stage in your development. The labeling decision is taken at the end of the review process and it involves array of experts from the Agency including product quality team.

Meeting Discussion:
No further discussion required.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no specific issues requiring further discussion at this time.

4.0 ACTION ITEMS

There are no specific due dates or time lines for submission of information or other action items. General agreements and commitments are included in the Discussion section (2.0) above.

5.0 ATTACHMENTS AND HANDOUTS

Handout provided by Rockwell Medical, Inc. on November 25, 2013, see attached.

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

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/s/

ALI H AL HAKIM
11/26/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 51290

MEETING MINUTES

Rockwell Medical, Inc.
Attention: Mr. James Hinson
Head of Regulatory Affairs
Rockwell Medical, Inc.
30142 Wixom Road
Wixom, MI 48393

Dear Mr. Hinson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for *Triferic* (Soluble Ferric Pyrophosphate).

We also refer to the meeting between representatives of your firm and the FDA on September 9, 2013. The purpose of the meeting was to discuss with the Agency the content and format for a planned New Drug Application (NDA) for Soluble Ferric Pyrophosphate.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Theresa Carioti, Regulatory Project Manager at (301) 796-2848.

Sincerely,

{See appended electronic signature page}

Kathy Robie Suh, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	September 9, 2013 9:00 – 10:00 AM
Meeting Location:	White Oak Building 22, Room 1311
Application Number:	IND 51290
Product Name:	*Triferic* (Soluble Ferric Pyrophosphate)
Indication:	Iron replacement product for the treatment of iron loss and maintenance of hemoglobin in adult patients with hemodialysis dependent chronic kidney disease
Sponsor/Applicant Name:	Rockwell Medical, Inc.
Meeting Chair:	Kathy Robie Suh, MD, PhD
Meeting Recorder:	Theresa Carioti, MPH

FDA ATTENDEES

Division of Hematology Products (DHP)
Edvardas Kaminskas, MD, Deputy Division Director
Kathy Robie Suh, MD, PhD, Clinical Team Leader
Min Lu, MD, Clinical Reviewer
Qin Ryan, MD, PhD, Safety Medical Officer
Diane Leaman, BS, MT (ASCP), Safety Project Manager
Laura Wall, MS, BSN, Regulatory Project Manager
Theresa Carioti, MPH, Regulatory Project Manager

Division of Hematology Oncology Toxicology (DHOT)
Haleh Saber, PhD, Supervisory Pharmacologist
Pedro Del Valle, PhD, Pharmacology/Toxicology Reviewer

Office of New Drug Quality Assessment (ONDQA)
Ali Al-Hakim, PhD, Branch Chief
Janice Brown, MS, Chemistry, Manufacturing & Controls Lead
Debasis Ghosh, PhD, Product Quality Reviewer

Office of Clinical Pharmacology (OCP)
Julie Bullock, PharmD, Clinical Pharmacology Team Leader
Elizabeth Shang, PharmD, Clinical Pharmacology Reviewer

Office of Biostatistics (OB), Division of Biometrics (DB)
Lei Nie, PhD, Biometrics Team Leader
Qing Xu, PhD, Biometrics Reviewer

Office of Business Informatics (OBI) CDER E-Data group
Lisa Lin, IT Project Manager

SPONSOR ATTENDEES

Rockwell Medical
Robert L. Chioini, President and CEO
Raymond Pratt, MD, Chief Medical Officer
Ajay Gupta, MD, Chief Scientific Officer
James Hinson, Head of Regulatory Affairs
Rameshwar Shukla, PhD, Director CMC
Carrie Guss, Sr. Director, Clinical Operations
Vivian Lin, MD, Sr. Director, Clinical

Consultants (for Rockwell Medical)
(b) (4) Toxicologist (b) (4)
(b) (4) Principal Investigator CRUISE studies
(b) (4), Sr. Statistician (b) (4)

1.0 BACKGROUND

Rockwell Medical requested a pre NDA meeting on June 7, 2013 to discuss Soluble Ferric Pyrophosphate (SFP). The objective of the meeting is to reach agreement on the content and format of the NDA. An NDA submission is planned for the end of 2013.

Triferic™ is the proprietary name for SFP, which the sponsor defines as a new chemical entity. SFP is a complex iron salt that is added to dialysate and crosses the dialyzer membrane and enters the blood, providing a slow, measured, continuous transfer of the iron complex to the patient during the course of their dialysis treatment, in contrast to the intermittent bolus delivery used with IV macromolecular iron complexes. In addition, SFP delivers iron together with pyrophosphate, an anion that facilitates transferrin uptake and physiological iron delivery to the erythron.

Rockwell Medical is completing the first, pivotal clinical study in its development program and topline results will be available soon. Additionally, Rockwell Medical reports that a second, pivotal study (identical design) is completing within approximately 8 weeks.

The pre NDA meeting occurred on September 9, 2013.

2. DISCUSSION

2.1. Quality Questions

Question Q1:

Background: Release testing and stability specifications for drug substance and drug product are contained within the meeting materials (**Section 12**).

Question Q1: Does the Division have any concerns, with regard to NDA filing and approval, about the testing methodologies or release/stability specifications?

FDA Response to Question Q1: ***We have following comments on the filing, approval, testing and specifications issues:***

- ***NDA Filing: Final decision on the filing issues will be determined at the time of NDA filing review. You have not provided adequate CMC information in the meeting package to confirm the adequacy of the CMC information for NDA filing.***
- ***NDA Approval: The decision on NDA approval will be determined at the time of NDA review (see additional comments below).***
- ***Testing methodologies: For all non-compendial methods, provide validation report in the NDA.***
- ***Drug Substance/Drug Product Release/Stability Specifications: The critical quality attributes listed in drug substance/drug product release/stability specifications are reasonable. However, the specification for each attribute should be properly***

justified in the NDA. The adequacy of the specifications will be determined at the time of NDA review.

- ***Additional Comments:***
  1. ***Harmonize the drug substance release and stability specifications for 'Assay Iron' and 'Assay Anion Content'.***
  2. ***Provide product compatibility and stability data in support of the use of low density polyethylene (b) (4) as primary packaging material in the container closure system manufactured by (b) (4) Technology.***

Meeting Discussion: No discussion occurred.

Question Q2: Sponsor requested to remove this question; however, the Agency is providing responses below.

Background: Rockwell prepared 8 lots of API and 4 lots of drug product (5 mL, low density polyethelene (LDPE) vials manufactured by Holopack). These drug product lots were shown to be stable for 24 months at 25 °C±2°C, 60% RH. (b) (4)

(b) (4)

Question Q2 (a): (b) (4)

FDA Response to Question 2a: No.

Meeting Discussion: No discussion occurred.

Question Q2 (b): Does the Division agree that the submission of additional stability data for this drug product is a minor submission not extending the review clock?

FDA Response to Question 2b: No.

Meeting Discussion: No discussion occurred.

2.2. Nonclinical Questions

Question 3:

Background: The NDA submission will include chronic repeat-dose toxicity studies SFP in rats and dogs and a 3-test battery of genotoxicity studies. Chronic administration of SFP to

rats and dogs did not produce hyperplastic or preneoplastic lesions, the genotoxicity studies indicated that SFP does not present a genotoxic hazard to humans, and published lifetime rodent carcinogenicity studies with other iron containing compounds indicate that such compounds do not present a carcinogenic hazard to humans. Consequently, Rockwell believes that the weight of evidence indicates that SFP does not pose a carcinogenic hazard to human subjects and that no carcinogenicity studies with SFP are necessary for NDA filing.

Question3: Does the Division concur that no carcinogenicity studies are necessary for NDA filing?

FDA Response to Question3: ***We agree that carcinogenicity studies with SFP are not needed.***

Meeting Discussion: No discussion occurred.

Question 4:

Background: The NDA submission will contain a complete toxicology assessment of SFP to include acute and chronic repeat-dose toxicity studies SFP in rats and dogs, a 3-test battery of genotoxicity studies, and Segment I, II and III reproductive and developmental toxicity studies. The results of the nonclinical program are summarized in the meeting materials (**Section 11**). Rockwell believes this program supports the NDA filing.

Question 4: At this time, does the Division agree this program supports the NDA filing?

FDA Response to Question 4: ***Your nonclinical program is acceptable. A decision on the adequacy of the studies will be made after review of data submitted with the NDA.***

Meeting Discussion: No discussion occurred.

2.3. Clinical Questions

Question 5:

Background: The topline results of the first pivotal phase 3 study (CRUISE 1) are summarized in the meeting materials (**Section 10.3.3**). CRUISE 1 demonstrated that SFP is efficacious based on the primary endpoint.

Question 5: Assuming the efficacy results are reproduced in the second pivotal CRUISE 2 study (identical design), does the Division believe these two pivotal studies are sufficient for NDA filing (barring other RTF issues)?

FDA Response to Question 5: ***It will be determined at the filing meeting after the NDA is submitted. Two adequate and well-controlled studies are generally required to support an indication. Based on your summary, in CRUISE 1 study, a significant proportion of study***

patients were withdrawn from the study (SFP 45.4% and placebo 53.6%) which resulted in a mean duration of participation in randomized treatment period of 23 weeks for the planned 48-week study. This raises concerns for intended long-term use of SFP in patients undergoing hemodialysis. You need to provide justifications for clinical utility of your product.

Meeting Discussion: The sponsor explained that the discontinuations in the CRUISE 1 study were not result of lost to follow-up. Most patients were transitioned into an open label follow-on due to the study design (ESA dose clamped). The sponsor explained that the PRIME study better reflects current clinical practice where ESA doses are allowed to be adjusted. The Division commented that consideration of these factors will be a review issue.

Question 6:

Background: The results of the clinical program and ongoing studies are summarized in the meeting materials (**Section 10.3**). This program has consisted of five Phase 1 or 2 studies, a supportive Phase 2b study (PRIME), two pivotal clinical studies (CRUISE 1 and CRUISE 2) and a large safety study (RMTI-SFP-6). Rockwell believes this program is sufficient for the NDA filing and approval.

Question 6 At this time, does the Division agree this program is sufficient for the NDA filing and approval?

FDA Response to Question 6: See response to Question 5. The sufficiency of data for the NDA filing and approval will be a review issue.

Include an evaluation of the effects of intrinsic (e.g. age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) and extrinsic factors (e.g. drugs, herbal products, diet, smoking, and alcohol use) on your product's exposure, efficacy, and safety properties in your NDA submission.

Meeting Discussion: No discussion occurred.

Question 7:

Background: Within the clinical trials, no patients with severe liver disease were studied. Patients with severe liver disease have low albumin and transferrin levels. (b) (4)

Question 7: Does the Division agree that studies in patients with severe liver disease on hemodialysis are not necessary for NDA filing or approval?

FDA Response to Question 7: ***Questions of fileability and approval will be review issues and determinations will be made after NDA filing. It is our expectation that the NDA is complete upon submission including all Clinical Pharmacology Studies. Please summarize your data in patients with mild and moderate hepatic impairment.***

Regarding your product, in the absence of an ADME data that justifies waiving a trial in patients with hepatic impairment, you should plan on conducting and completing a hepatic impairment trial. Please refer to the Guidance for Industry Pharmacokinetics in Patients with Impaired Hepatic Function.

Meeting Discussion: The sponsor has some trials ongoing that will help describe the clearance of SFP. Whether or not additional trials are needed in patients with mild or moderate impairment will be a review issue. The sponsor will provide their justification for why they think hepatic impairment will not affect SFP clearance.

Question 8:

Background: The clinical trial program did not include hemodialysis patients who were less than 18 years of age. In accordance with the recent draft guidance on pediatric studies, Rockwell will submit a draft pediatric plan in the NDA and request a deferral of this requirement.

Question 8: Does the FDA concur that pediatric studies are not necessary for NDA filing?

FDA Response to Question 8: ***Yes. Your proposal is acceptable.***

Meeting Discussion: No discussion occurred.

Question 9:

Background: The NDA will contain an Integrated Summary of Efficacy (ISE) in Module 5.3.5.3. The ISE will integrate the efficacy data from the two identical pivotal studies (CRUISE 1 and CRUISE 2) and include a discussion of the results of the major supportive study, PRIME. A draft of the ISE statistical analysis plan (SAP) and sample report tables are presented in the meeting materials (**Section 13.2**).

Question 9: Does the Division agree with the proposed format and content of the ISE?

FDA Response to Question 9: ***The analysis of ISE should be stratified by study. ITT population should also be used as the primary efficacy analysis for each individual pivotal study. Only stratified variables should be included in the ANCOVA model. ANCOVA model with other covariates should be considered as supportive analysis only.***

Meeting Discussion: No discussion occurred.

Question 10:

Background: The NDA will contain an Integrated Summary of Safety (ISS) in Module 5.3.5.3. The ISS will integrate the safety data from the controlled phases of two identical pivotal studies (CRUISE 1 and CRUISE 2), and the major supportive study (PRIME) for a Controlled Studies grouping. An All Studies grouping will include all safety data for subjects who received at least one dose of SFP in a Phase 2 or 3 study plus data available at the time of the NDA cut-off date for the on-going, open-label, uncontrolled extension phases of the above studies. Safety data from two Phase I studies will be presented separately and not integrated. A draft of the ISS statistical analysis plan and sample report tables are presented in the meeting materials **(Section 13.2)**.

Question 10: Does the Division agree with the proposed format and content of the ISS?

FDA Response to Question 10: Yes. The proposal is acceptable.

Meeting Discussion: No discussion occurred.

Question 11:

Background: For planning purposes, the open-label, uncontrolled phases of the previously mentioned studies (in the question C6) are completing in 1Q2014. The 120-day safety report will consist of updated summaries of the All Studies grouping. The summaries will present the NDA data and the safety update side by side for ease of comparison.

Question 11: Does the Division find this proposal suitable for planning the 120-day safety update?

FDA Response to Question 11: Yes. The proposal is acceptable.

Meeting Discussion: No discussion occurred.

Question 12:

Background: (b) (4)

[redacted]

Question 12: Will the Division support incorporating the results of this study in the Clinical Pharmacology section of the product labeling as supporting data for the primary effect?

FDA Response to Question 12: ***Whether results of any trial will be incorporated into the product labeling will be a review issue.***

Meeting Discussion: **No discussion occurred.**

Question 13:

Background: The total database in the NDA will consist of drug exposures of about 1450 patients in total, of which 400 patients would have been exposed for at least 6 months and 100 patients for at least 1 year (**Table 18**). Most of these exposures are from long term, chronic thrice weekly dosing of outpatient hemodialysis dependent CKD patients. This safety database represents over 400 patient-years of exposure. The exposure is consistent with the ICH guidance for chronic dosing suggesting about 1500, 300-600, and 100 patients exposed, overall, for 6 months, and for 1 year, respectively. Rockwell believes this exposure is sufficient to define the safety profile of SFP.

Question 13: Does the Division concur that this safety database is sufficient for NDA filing and approval?

FDA Response to Question 13: ***The sufficiency of safety data will be a review issue.***

Meeting Discussion: **No discussion occurred.**

2.4. NDA Format and Content Questions

Question 14:

Background: Rockwell intends to submit an XML-based eCTD formatted NDA with a vendor who is validated for the Electronic Submission Gateway. The proposed table of contents is contained within the meeting materials (**Section 13.1**).

Question 14: Does the Division have any concerns with this format or table of contents?

FDA Response to Question 14: ***From a technical standpoint (not content related) yes, the proposed format for the planned NDA is acceptable. However, please see additional comments below.***

- ***Please include technical point of contact in your cover letter.***
- ***Provide the reviewer note as a separate document from the cover letter and also, it will be helpful to reviewers if the referenced sections are hyperlinked***
- ***When you submit word documents, make sure the leaf title includes "word", so reviewers could quickly identify the word version of the document and if possible, also include "spl" in the leaf title of the SPL document.***

- ***The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 (tabular format), should be linked to the referenced studies in m5.***
- ***Providing a single 3.2.S and 3.2.P Manufacturing section with attribute of "ALL" and differentiating documents by leaf title, is acceptable. Additionally, indicating the substance/product/manufacturer name at the beginning of a leaf title helps sorting abilities when sorting by substance, product or manufacturer.***
- ***The study ID for the BIMO STF in m5.3.5.4 should be "bimo."***
- ***It is recommended, but not required, that a BIMO Reviewer's Guide (in PDF format) be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.***

Other Comments regarding format and contents:

- ***Datasets should have one and only one unique subject ID for each patient among all trials. Variables used in the define datasets should be the same for all datasets so that they can be combined or sorted as needed for cross study evaluations (i.e., one definition, well-annotated, per one variable).***
- ***Provide a roadmap to locations of major topics in the submission.***

Question 15:

Background: The planned NDA data cut-off date (August 19, 2013) for the NDA is similar to the IND Annual Report cut-off date (September 11, 2013). Because the NDA will be all inclusive of the available data and redundant with the IND Annual Report, Rockwell requests (b) (4)

Question 15: Does the Division agree?

FDA Response to Question 15: No. You need to submit IND annual report with reference to the NDA submission.

Meeting Discussion: No discussion occurred.

Question 16:

Background: While it is customary to submit CRFs for all deaths, SAEs and discontinuations due to adverse events, due to the large numbers of events in the study population, we propose to submit (b) (4)

Question 16: Does the Division find this CRF proposal acceptable for filing?

FDA Response to Question 16: ***No. You need to submit CRFs for all deaths, SAEs, and discontinuations due to adverse events.***

Meeting Discussion: Sponsor asked for confirmation regarding the submission of all CRFs (as described above), except for prior to randomization.

Question 17:

Background: Rockwell proposes to not provide patient profiles/CRTs in the NDA. Study data will be provided as CDISC compliant SDTM and ADaM datasets for use of the clinical reviewers (**Section 13.1**). Patient profiles can be generated from these datasets by JMP Clinical or J-Review.

Question 17: Does the Division agree with this proposal?

FDA Response to Question 17: ***No. You need to provide patient narratives for all deaths, SAEs, and discontinuations due to adverse events.***

Meeting Discussion: Sponsor commented that they have one early legacy study (SFP-1) for which information to complete a narrative is not available. Sponsor confirmed they have narrative data for the phase 3 trials. Sponsor will provide explanation for the lack of narratives for the legacy study mentioned above in their NDA submission.

Post-meeting clarification: Narratives do not need to be provided for patients who experienced death, SAEs or discontinuation due to adverse events prior to randomization.

Question 18:

Background: (b) (4)

Question 18: Does the Division agree that priority review is warranted?

FDA Response to Question 18: ***The decision will be made at filing meeting.***

Meeting Discussion: No discussion occurred.

Question 19:

Background: Rockwell plans to submit BIMO datasets at the time of the NDA filing. These datasets will be for the CRUISE 1, CRUISE 2 and PRIME studies. Per the Guidance, the ITT population will be used; this population will be defined as all randomized subjects. For subjects who did not receive drug or who had no post-baseline values, the baseline value will be used for the primary efficacy parameter. Also, the Guidance states that all adverse events should be counted, including those that are not treatment emergent. This is assumed to include events that occurred prior to study drug (for example during Stage 1 of CRUISE) for subjects in the ITT population (**Section 13.1**).

Question 19 (a): Does the Division concur that these are the only studies for which BIMO datasets are needed?

FDA Response to Question 19 (a): Yes. It is acceptable.

Meeting Discussion: No discussion occurred.

Question 19 (b): Does the Division concur with the proposed method for including ITT subjects with no post-baseline efficacy data?

FDA Response to Question 19 (b): Yes. It is acceptable.
Please perform sensitivity analyses to assess the limitation of the data and to examine the potential impact of any missing data.

Meeting Discussion: The FDA clarified that the sensitivity analysis refers to the pivotal phase 3 studies. This does not refer to the BIMO datasets.

Question 19 (c): Does the Division concur that adverse events that occurred prior to study drug should be counted for subjects in the ITT population?

FDA Response to Question 19 (c): Yes. We agree.

Question 20:

Background: Rockwell proposes to provide the statistical programs used to generate the inferential analyses for CRUISE 1, CRUISE 2 and PRIME studies as well as for the ISE. We also propose to provide the programs used to create the ADaM datasets for these studies.

Question 20: Does the Division agree that these are the only source programs required for the NDA submission?

FDA Response to Question 20: ***The proposal is acceptable, but please provide the following information:***

- ***Please provide all programs (e.g. SAS programs) that were used to create all of the efficacy and safety tables and figures included in the main test portion of the CSR. Please also provide all necessary macros and utility programs. All programs should be thoroughly commented:***
  - ***Please include an index of the programs that were used to produce all of the efficacy and safety tables and figures in the main test portion of the CSR.***
  - ***Please ensure that the dataset file names are consistent with those in the programs that call them, so that the Agency can run the programs smoothly to verify the results/figures/tables reported in the submission.***
  - ***Please include annotations for all efficacy and safety tables and figures in the main test portion of the CSR. The annotations should indicate which analysis dataset variables were used to produce the table or figure.***
- ***Please provide a Statistical Efficacy Analysis Data Set, in SAS transport format to our Electronic Document Room (EDR). This dataset shall have one record only per subject and need to include at least the following information:***
  - ***Demographic variables***
  - ***Baseline characteristics***
  - ***Population flags (ITT, PP, subjects who completed the study, etc.)***
  - ***Efficacy outcomes (primary, secondary, etc.)***
  - ***Covariates and subgroup variables***
  - ***Subject disposition variables***
- ***The define.pdf file should contain the descriptions of variable names on data sets. All derived variables should be clearly defined so that these variables can be traced to variables in the raw datasets. Please also include the programs that were used to derive the dataset.***
- ***Additionally, there should be an instruction for the reviewer for the use of variables and flags to identify the set of patients on which the primary analysis was performed.***

Meeting Discussion: No discussion occurred.

Additional Clinical Pharmacology Comments:

1. **We reiterate our previous Clinical Pharmacology comment regarding the use of a validated analytical method to determine iron concentrations.**
2. **In the appropriate clinical pharmacology sections of the eCTD include the following:**
   - **An evaluation of the effects of covariates such as age, weight, gender, race, etc. on the PK (pharmacokinetics) of soluble ferric pyrophosphate (SFP).**
   - **Datasets for clinical pharmacology and biopharmaceutics studies should be complete and not be limited to PK/PD. For example, domains related to safety (e.g., ADR's), demographics, non-PK laboratory values, concomitant drug use should be included. All of these are important in identifying patterns of potential clinical pharmacology related causes of clinical safety outcomes.**

- **Provide all concentration-time and derived PK parameter datasets for all studies. In the study reports, present the PK parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate.**
- **Provide a table listing of patients with renal or hepatic impairment who have received SFP, organized by trial number. Include available renal and hepatic function parameters such as SCr, CLCr calculated by the Cockcroft Gault equation (or eGFR calculated by MDRD), AST/ALT, T.Bili, platelet count, etc for each patient in the listing. Also, provide summaries of the following information for each patient: PK and PD data, safety, and clinical efficacy.**

Additional CMC comments:
At this time, we do not accept that this product qualifies as a "new molecular entity," Therefore, this application will not be subject to "the Program" under PDUFA V.

Meeting Discussion: The FDA will check whether new formulations are subject to the PDUFA V program. The sponsor will provide additional justification for NME in their NDA application.

Post Meeting Addendum: After further internal discussion following your face-to-face meeting on September 9, 2013, the Agency does not consider new formulation to be an NME. As stated in the PDUFA V reauthorization goals and procedures, only NMEs are considered for "the Program".
http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf

3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting held on or after November 6, 2012. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and

any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the following labeling review resources: the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, labeling guidances, and a sample tool illustrating the format for Highlights and Contents (Table of Contents) available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

4.0 ISSUES REQUIRING FURTHER DISCUSSION

During the face-to-face meeting, the sponsor requested additional clarification regarding whether new formulations are considered part of the PDUFA V "Program." We have confirmed that only NME applications are part of "the Program."

After reviewing your justification and rationale for NME assignment, we conclude, that because your soluble ferric pyrophosphate product does not contain an active moiety that has never been approved by FDA or marketed in the US, your product does not qualify as an NME.

5.0 ACTION ITEMS

The sponsor was advised to request a pre NDA CMC-only meeting with the Office of New Drug Quality Assessment (ONDQA).

6.0 ATTACHMENTS AND HANDOUTS

None

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

/s/

KATHY M ROBIE SUH
09/19/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 51,290

MEETING MINUTES

Rockwell Medical Technologies
Attention: Mark Ammann, Pharm.D.
Vice-President, Regulatory Affairs
2200 Commonwealth Boulevard, Suite 100
Ann Arbor, MI 48105

Dear Dr. Ammann:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Soluble Ferric Pyrophosphate.

We also refer to the meeting between representatives of your firm and the FDA on June 30, 2010. The purpose of the meeting was to discuss the the results of Phase II studies, the design of the Phase III studies, the effect of SFP on the QT interval, and procedural issues related to the marketing application for this combination drug/device.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Trinh Scott, Regulatory Project Manager, at (301) 796-3311 or Trinh.Scott@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ann Farrell, MD
Director (Acting)
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration

Enclosure: Meeting Minutes Attached

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	EOP2
Meeting Date and Time:	June 30, 2010, 3:00 PM – 4:30 PM (EST)
Meeting Location:	WO, Building 22, Conference room 1315
Application Number:	IND 51,290
Product Name:	Soluble Ferric Phyrophosphate (SFP)
Indication:	For the (b) (4) treatment of iron deficiency anemia in hemodialysis patients; iron replacement in hemodialysis patients.
Sponsor/Applicant Name:	Rockwell Medical Technologies, Inc.
Meeting Chair:	Ann Farrell, M.D.
Meeting Recorder:	Trinh Scott, M.S.

FDA ATTENDEES

Division of Hematology Products
William Adams, Ph.D., CMC Branch Chief (Acting), ONDQA
Janice Brown, Ph.D., CMC Team Leader, ONDQA
Julie Bullock, Pharm.D., Clinical Pharmacology Team Leader, OTS
Jeffrey Cooper, M.S., D.V.M., Veterinary Medical Officer, CDRH
Virginia Elgin, M.D., Pediatric & Maternal Health Reviewer, PMHS
Ann Farrell, M.D., Director (Acting), DHP
Monica Fiszman, M.D., Ph.D., IRT Clinical Reviewer, DCRP
Debasis Ghosh, Ph.D., CMC Reviewer, ONDQA
Patricia Love, M.D., M.B.A., Deputy Director, Office of Combination Products
Min Lu, M.D., M.P.H., Clinical Reviewer, DHP
Todd Palmby, Ph.D., Pharmacology/Toxicology Reviewer, DHP
Kathy Robie Suh, M.D., Ph.D., Clinical Team Leader, DHP
Mark Rothmann, Ph.D., Biostatistics Team Leader, OTS
Haleh Saber, Ph.D., Pharmacology/Toxicology Team Leader, DHP
Trinh Scott, M.S., Regulatory Project Manager, DHP
Qing Xu, Ph.D., Biostatistics Reviewer, OTS
Hao Zhu, Ph.D., IRT-QT Scientific Lead, DCRP

SPONSOR ATTENDEES

Rockwell Medical Technologies, Inc.
(b) (4), Regulatory Affairs (Consultant)

(b) (4), Clinical (Consultant)
Robert Chioini, Chief Executive Officer
Ajay Gupta, M.D., Chief Scientific Officer
Carrie Guss, Senior Director, Clinical Research
(b) (4) Biostatistics (Consultant)
Thomas Klema, Vice President, Chief Financial Officer
(b) (4) Cardiac Safety and QTc Effects (Consultant)
Richard C. Yocum, M.D., Vice President, Drug Development & Medical Affairs

1. BACKGROUND

In a letter dated May 3, 2010, Rockwell Medical Technologies, Inc. requested an End of Phase II meeting to discuss the the results of their Phase II studies, the design of the Phase III studies, the effect of SFP on the QT interval, and procedural issues related to the marketing application for this combination drug/device. In a submission dated June 1, 2010, Rockwell Medical Technologies, Inc. submitted the meeting background package. On June 28, 2010, FDA sent Rockwell Medical Technologies Inc., via email, draft preliminary responses to the questions raised in the June 1, 2010 background materials (see questions and responses below).

2. DISCUSSIONS

On June 29, 2010, Rockwell indicated via email that they would like to prioritize discussion of the meeting to these Questions: 4, 18, 9, 6, 3, 11, 13, 12, 15, 14, 17, 8, 1, and 7. All other FDA responses were acceptable to Rockwell.

The actual meeting discussions were concentrated on Questions 4, 11, and 12.

2.1. CMC

QUESTION 1

Additional investigation of GMP SFP drug substance: Rockwell submitted a CMC amendment to IND 51,290 on 10 May 2010 for the new GMP SFP. The GMP SFP material was also described in a briefing document for Rockwell's 29 September 2009 Type C meeting. The only technical issue raised about the GMP material was a higher (b) (4) *content relative to food-grade SFP. The* (b) (4) *content has been subsequently addressed, such that the* (b) (4) *content in the GMP SFP has been reduced* (b) (4) *% and is now much closer to the range of the food-grade SFP that has been studied in previous clinical trials (see* ***Section 8****). Assuming no adverse safety signals for GMP SFP in the pending clinical bridging study, Rockwell would propose additional CMC investigation of GMP SFP drug substance be limited to ICH stability and other nominal routine increases in CMC information needed for the marketing application. Does FDA agree?*

FDA Response:

From the CMC perspective, GMP-grade drug substance is acceptable for the use in the proposed clinical studies. In absence of any batch information of clinical drug product, drug product quality can't be determined. To establish safety, the clinical drug product for Phase III must pass the proposed acceptance specification.

The adequacy of CMC information will be determined at the time of NDA review.

The following additional CMC issues need to be addressed at the time of NDA submission:

- **Based on your submission, drug substance release specification for Heavy Metals (NMT (b) (4) ppm for any single element) is not acceptable. Provide a specification for each element with proper justification for intended test population.**
- **Develop and validate an assay method to measure iron content in the admixture.**
- **Provide at least 12 months long-term stability data for drug product.**
- **Provide an assay method for (b) (4) with a limit of detection at or below the (b) (4) ppm level.**
- **Describe how bioburden is controlled during the (b) (4) hour storage period.**

2.2. CLINICAL

QUESTION 2

*Adequacy of Phase II safety data: Rockwell believes that the accumulated clinical safety data for SFP (see **Sections 10.1.2, 10.1.3, and 10.1.4**), combined with the anticipated completion of the safety bridging clinical trial (see **Section 10.1.5**) with no findings of any safety concern, (all conducted in the targeted CKD-HD patient population for Phase III) are adequate to support proceeding to the Phase III clinical program and initiation of the proposed Phase III trial design as proposed (see **Section 10.5** and **Appendix E**). Does the FDA agree?*

FDA Response:

We agree that the safety data appear sufficient to proceed to Phase 3 study. However, the treatment duration is much shorter in your completed phase 2 studies (~4 months) than in the proposed phase 3 studies (12 months). Close safety monitoring including TSAT, ferritin level, and adverse events during the treatment will be needed in your phase 3 studies.

With regard to initiation of the proposed Phase 3 trial design, we are concerned about your proposed change in primary efficacy endpoint as discussed in our response to Question #4 below.

QUESTION 3

Adequacy of dose selection data: (b) (4)

Does the FDA agree?

FDA Response:

No, we disagree. (b) (4) **Please justify your interpretation of the study results and conclusions that your treatment and dose would be beneficial to patients.**

QUESTION 4
Primary efficacy endpoint: (b) (4)

FDA Response:
No, we do not agree. (b) (4) **An endpoint that assesses a benefit such as increase or maintenance of hemoglobin level or improvement of clinical outcomes should be considered as the primary efficacy endpoint in your phase 3 studies. You may consider the change in ESA dose as a secondary endpoint in your phase 3 trials.**

Rockwell Response (6/28/10):
(b) (4)

Refer to Page 398 of our Briefing Book

Minutes of November 17, 1997 meeting:

"3C. Phase III studies must utilize clinical primary efficacy endpoints. The proposed surrogate endpoints, such as a decrease in iron dextran utilization, must be changed to efficacy endpoints which provide evidence of clinical effect, such as maintenance of hemoglobin **or a decrease in erythropoietin** or transfusion **requirements**. A composite primary endpoint may be developed and treatment groups compared for success/failure and time to success."

Refer to Page 417 of our Briefing Book
Minutes of June 12, 2006 meeting:

- "Dr. Shashaty provided the group with a brief history of this product within DMIHP to include a summary of correspondences and meetings between them. A brief discussion about endpoints took place. As communicated to Rockwell in previous discussions with DMIHP, **efficacy endpoints for phase 3 studies should include clinically meaningful measures such as** maintenance of hemoglobin, **decrease in EPO use** or decrease in transfusion requirements."

Discussion (6/30/10):
The Sponsor and the Agency had a wide ranging discussion regarding endpoints and trial designs and patient populations. (b) (4)

(b) (4)

QUESTION 5

(b) (4)

FDA Response:
No, we do not agree. See response to Question #4.

QUESTION 6

(b) (4)

*(see **Protocol Section "Data Analysis,"** **Page 26** in **Appendix E**). Does the FDA agree?*

FDA Response:
No. See response to Question #4.

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QUESTION 7

*Study blinding: The Phase III study design is proposed to be double-blinded (see **Appendix E**). Specifically, during the randomized, parallel group, Stage 2 of the study comparing SFP to placebo, all study patients, the Sponsor, the independent centralized Anemia Management Center, and all investigative site staff with the exception of the person preparing the SFP in bicarbonate concentrate will be blinded to the treatment group assignment. Does the FDA agree that this level of blinding is acceptable for the Phase III program?*

FDA Response:
A double-blind trial is one in which neither the subject nor any of the investigator or sponsor staff involved in the treatment or clinical evaluation of the subjects are aware of the treatment received. This should include anyone determining subject eligibility, evaluating endpoints, or assessing compliance with the protocol. The person preparing the SFP in bicarbonate concentrate can be unblinded if he has no association with sponsor, subjects, or investigators. It is the responsibility of the sponsor to provide procedures to ensure the maintenance of the blind and to adequately document compliance with those procedures.

QUESTION 8

(b) (4)

(b) (4)

(b) (4)

(b) (4)

FDA Response:

No, the analysis should be based on the intent-to-treat population and all patients should be measured for primary endpoint. A proper primary endpoint should capture a clinical outcome from all patients. Sensitivity analyses should be performed to examine the potential impact of any missing data.

Analyses performed on other populations may be considered as supportive.

QUESTION 9

Generalizability of Phase III data

(b) (4)

(b) (4)

Does the FDA agree?

FDA Response:
No, we do not agree. See response to Question #4.

QUESTION 10
*Adequacy of Phase III design to support efficacy label claim: Does the FDA agree that the proposed Phase III design (see **Appendix E**) is adequate to support an efficacy claim for NDA approval if the findings of the study are found by FDA to be sufficiently favorable?*

FDA Response:
No, we do not agree. See responses to Questions #3 and #4.

2.3. CARDIAC SAFETY AND THOROUGH QT/QTC (TQT) STUDY

QUESTION 11
*Cardiac safety and TQT study: Rockwell believes that the requirement for a thorough QT/QTc (TQT) study has been satisfied by the integrated assessment of cardiac risk provided by the data from the preclinical and clinical SFP studies completed to date, based on the following rationale (see **Section 10.2** for full details and discussion). As supported by the bulleted points below, does the FDA agree that SFP has been shown to not affect electrocardiogram (ECG) intervals and that no further investigation of SFP effect on ECG intervals is warranted in order to satisfy the TQT requirement?*

FDA Response:
We cannot agree without reviewing data for Study RMTI-SFP-2, which is intended to be the substitute for a TQT.

When you submit the "QT study" report, please include the following items:

a. **Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed.**
b. **Electronic copy of the study report.**
c. **Electronic or hard copy of the clinical protocol.**
d. **Electronic or hard copy of the Investigator's Brochure.**
e. **Annotated CRF.**
f. **A data definition file which describes the contents of the electronic data sets.**

g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses.

h. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate HR, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable).

i. Data set whose QT/QTc values are the average of the above replicates at each nominal time point.

j. Narrative summaries and case report forms for any:

- **Deaths**
- **Serious adverse events**
- **Episodes of ventricular tachycardia or fibrillation**
- **Episodes of syncope**
- **Episodes of seizure**
- **Adverse events resulting in the subject discontinuing from the study**

k. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com).

l. A completed Highlights of Clinical Pharmacology Table.

Advancing in this field – and possibly reducing the burden of conducting QT studies – depends critically upon obtaining the most comprehensive understanding of existing data. Please consider making your data, at least placebo and positive control data, available for further research purposes; see, for examples, the Data Request Letter at www.cardiac-safety.org/library.

Rockwell Response (6/28/10):

In your response, you indicate "We cannot agree without reviewing data for Study RMTI-SFP-2, which is intended to be the substitute for a TQT." In our briefing book, we provided a summary (section 10.2.5, pages 145-167) and over 80 pages of detailed data tables (Appendix B, pages 249-332) to describe the ECG results from Study RMTI-SFP-2.

I also want to make reference to two e-mails to you on this subject (April 30, 2010 and May 20, 2010) seeking confirmation that IRT would be able to review this package in advance of the meeting on June 30th. On May 24th you responded "I have consulted with the IRT regarding Question #11 in your meeting request, and have requested their presence at the meeting. I have not gotten feedback from them yet, probably not until they have had a chance to look at the background package." From this, we have assumed that IRT would be reviewing the background material provided.

We believe that this data is sufficient for the Division and IRT to provide a provisional response on whether the completed study has adequately evaluated the effect of SFP on QT . As such, could you please confirm that the Agency has reviewed this data, and that it is primarily a matter of sending supportive information such as electronic datasets and reports so that FDA can validate the results.

Discussion (6/30/10):
The need for further intensive ECG monitoring in Phase 3 will be determined after review of data from the RMTI-SFP-2 study. The Sponsor will submit the above data as requested along with a proposed plan for Phase 3 ECG monitoring. In addition, the Agency requested the Sponsor submit preclinical study reports.

2.4. REQUIREMENT FOR PEDIATRIC TRIALS

QUESTION 12
Pediatric plan for SFP clinical program: For the anticipated NDA submission of SFP, (b) (4) (b) (4) *Does the FDA agree that this pediatric plan is acceptable?*

FDA Response:
No. Although the number of pediatric patients on hemodialysis is small, these patients are treated in dedicated hemodialysis centers and receive multiple treatments per week, providing sufficient opportunity to study an agent administered via the dialysate. A pediatric plan must be submitted which includes an outline of the studies you are planning to conduct (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) sufficient to evaluate dose, safety and efficacy. The pediatric plan must contain a timeline for the completion of these studies, including the date the protocol will be submitted, the date studies will be completed and the date study reports will be submitted.

We recommend that juvenile animal studies, when appropriate, be included in the pediatric plan and be conducted in a timely manner so not to impose undue delays in the conduct of the pediatric clinical program. You may justify why juvenile animal studies are not needed. See ICH M3(2) for additional information.

Discussion (6/30/10):
The Sponsor understands the need for pediatric development and anticipates requesting a PREA deferral at the time of submission. Approval for the adult

indication does not require completion of pediatric studies, however, may be contingent upon agreement to performance of appropriate pediatric studies.

2.5. MISCELLANEOUS CLINICAL

QUESTION 13

*Clinical safety database: Rockwell believes that the overall patient exposure to SFP presented in **Table 1**, based on estimates of duration of exposure as of the time of NDA submission and review, is adequate to support the PMA/NDA submission and approval for SFP. Does the FDA agree?*

FDA Response:

The adequacy of the clinical safety database to support the NDA will be contingent upon the study results.

QUESTION 14

*Dialyzer membranes: The accumulated broad experience with multiple types of dialyzers from different manufacturers analyzed from the Phase II study data (Study RMTI-SFP-2, see **Section 10.1.3.11**) shows no SFP effect on dialyzer reuse. However, in order to fully address all known and any remaining concerns the FDA may have, Rockwell has designed, prior to initiation of the Phase III trials at dialysis centers that reuse dialyzers, an in vitro study of SFP and dialyzers (see **Section 10.4** and **Appendix D**). Rockwell believes that if this in vitro study is conducted and shows no evidence of SFP effect on dialyzers, this finding, combined with the Study RMTI-SFP-2 data, provide adequate assurance that SFP can be used without restriction for any dialysis machine, membrane, and dialysate, and that no further investigation in this area is warranted unless an adverse effect of SFP on dialysis equipment is observed in ongoing or future clinical trials.*

Does the FDA agree?

FDA Response:

Supporting analyses of study data by type of machine, reused versus new dialyzers, and other important variables of the dialysis may help inform labeling.

Generally, the labeling for the product will reflect the clinical settings in which it has been evaluated. Also, it may be appropriate to identify the types/characteristics of tested dialyzers.

The SFP should be tested with each different dialyzer material and each reuse disinfectant. The proposed testing of sieving co-efficients and SFP retention on the membrane appears sufficient, but biocompatibility of the membrane should be investigated if the SFP adheres to the membrane. This testing is addressed in the Guidance document:

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM078470.pdf

QUESTION 15

Adequacy of data for characterizing study drug exposure: An objective of the Phase II Study RMTI-SFP-2 was to determine the amount of SFP transferred from dialysate to patient during a dialysis session by measuring inflow and outflow iron concentrations in the dialysate and performing an area-under-the-curve analysis. However, the assay for this objective failed to be reliable and did not provide meaningful data from the study, testing was abandoned partway through the study, (b) (4) *However, the intra-dialytic changes in serum iron and other iron parameters do provide clear quantitative data regarding the amount of SFP-derived iron transferred from dialysate to the patient (see **Section 10.1.3.4.3**). Rockwell believes that patient exposure to SFP is adequately characterized by the Phase II data for intra-dialytic changes in serum iron parameters such that the clinical program can proceed all the way to NDA submission and potential approval without a more exact quantitative measurement of the transfer of SFP-derived iron from dialysate to patient bloodstream. Does the FDA agree?*

FDA Response:

It is generally acceptable. However, the marketing application submission will likely need to include information about the impact of dialysis procedure such as the duration of each dialysis session and the dialysate flow rate on the intra-dialytic changes in serum iron and other iron parameters. Any large amount of interpatient variability in response will need to be explained. We recommend continued development of a validated assay to measure these parameters.

QUESTION 16

*Geriatric patient population: None of the SFP clinical trials imposed an upper age restriction on patient enrollment. In the largest of these trials, the Phase II Study RMTI-SFP-2 (see **Section 10.1.3**), 33.6% (44/131) of the enrolled patients were ≥ 65 years of age, and 11.5% (15/131) were ≥ 75 years of age. The target indication for SFP of CKD patients on hemodialysis is a disease that is present in, but not unique to, the elderly population. The proposed Phase III protocol design (see **Appendix E**) does not propose an upper age restriction on enrollment, and is anticipated to enroll a percent of patients ≥ 65 years of age that is similar to that of Phase II, and therefore an excess of 100 patients ≥ 65 years of age treated with SFP is anticipated to be included in the SFP NDA submission (see **Table 3**). Rockwell believes that no additional or special clinical evaluation is required for the geriatric patient population. Does the FDA agree?*

FDA Response:

Yes, we agree.

2.6. FINAL SFP DRUG PRODUCT CONFIGURATION

QUESTION 17

(b) (4)

FDA Response:

Please clarify which of the above presentations are planned for the initial marketing application submission.

(b) (4)

Provide complete CMC data including stability data for drug product in the container closure system following ICH Q1A(R2) at the time of NDA filing.

2.7. REGULATORY PATHWAY AND ADMINISTRATIVE QUESTIONS

QUESTION 18

Product label indication statement: Rockwell proposes the label indication statement for NDA approval of SFP: (b) (4)

(b) (4)

." *Does the FDA agree that this label indication wording is acceptable and would be supported by a positive outcome in the Phase III program as proposed in this briefing book?*

FDA Response:

No, we do not agree with the proposed indication statement, given that we do not agree with your primary efficacy endpoint.

In general, labeling wording will be contingent upon the study results.

Also, given the different configurations identified in Question #17, the indication statements may vary.

QUESTION 19

FDA reviewing division: Given the recent reorganization of DMIHP (split of Medical Imaging), will the Division of Hematology be the primary reviewing division for an NDA component of the marketing application for SFP?

FDA Response:

Yes.

QUESTION 20

(b) (4)

(b) (4)

Also, depending upon your clarifications to question 17, FDA may have additional comments on the marketing application.

QUESTION 21

(b) (4) *Based on the Division's review of the proposed Phase III study design and the outcome of this End-of-Phase II meeting, does the FDA believe that there is sufficient agreement on the study design that it would be appropriate for Rockwell to prepare and submit* (b) (4) *?*

FDA Response:
No. See responses to Question #3 and #4.

QUESTION 22

(b) (4)

FDA Response:
The decision will be made during the NDA filing meeting.

(b) (4)

3. ISSUES REQUIRING FURTHER DISCUSSION

None

4. ACTION ITEMS

None

5. ATTACHMENTS AND HANDOUTS

None

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-51290	GI-1	ROCKWELL MEDICAL TECHNOLOGIES INC	(b) (4)/FERRIC PYROPHOSPHATE

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

/s/

ANN T FARRELL
07/21/2010