

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205874Orig1s000**

**CHEMISTRY REVIEW(S)**

**NDA 205874**

**BRANDNAME**  
**(ferric citrate) Tablets**

**Keryx Biopharmaceuticals Inc.**

**Monica D. Cooper, Ph.D. (Drug Substance)**  
**Thomas Wong, Ph.D. (Drug Product)**

**Office of New Drug Quality Assessment**  
**(DNDQA1/Branch1)**

**Reviewed for the Division of Cardiovascular and Renal**  
**Products (HFD-110)**

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# Chemistry Review Data Sheet

1. NDA 205874
2. REVIEW #: 2
3. REVIEW DATE: 29-Jul-2014
4. REVIEWERS: Monica D. Cooper, Ph.D. (Drug Substance) and Thomas Wong, Ph.D. (Drug Product)
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA 205874	07-Aug-2013
Amendment #0002 (revised list of establishments)	21-Aug-2013
Amendment #0008 (response to 74-day letter CMC questions)	04-Nov-2013
Amendment #0027 (USAN update)	14-Feb-2014
Amendment #0028 (response to IR letter CMC questions)	04-Mar-2014
Amendment #0032 (response to IR letter Biopharmaceutics questions)	21-Mar-2014

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment #0042 (response to Discipline Review Letter)	11-Apr-2014
Amendment #0047 (additional response to Discipline Review Letter)	28-Apr-2014
Amendment #0049 (response to CMC comments prior to teleconference)	12-May-2014
Amendment #0050 (response to CMC comments after teleconference)	15-May-2014
Amendment #0051 (follow-up responses)	19-May-2014
Amendment #0051 (container labeling)	20-May-2014

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Amendment #0056 (follow-up responses)	01-Jul-2014
Amendment #0057 (follow-up responses)	14-Jul-2014

7. NAME & ADDRESS OF APPLICANT:

<b>Name</b>	Keryx Biopharmaceuticals Inc.
<b>Address</b>	750 Lexington Ave. 20 <sup>th</sup> Fl. New York, NY 10022
<b>Representative</b>	James Oliviero, Chief Financial Officer
<b>Telephone</b>	212-531-5970
<b>Fax</b>	212-531-5961
<b>E-Mail</b>	joliviero@keryx.com

8. DRUG PRODUCT NAME/CODE/TYPE:

<b>Proprietary Name</b>	PENDING – Zerenex has been rejected by DMEPA
<b>Non-Proprietary Name (USAN)</b>	Ferric citrate
<b>Code Names</b>	Ferric citrate coordination complex KRX-0502
<b>Chemistry Type</b>	2
<b>Submission Priority</b>	S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CAT./INDICATION: Iron-containing oral phosphate binder/Control of serum phosphate levels <sup>(b) (4)</sup>  
[REDACTED] in patients with chronic kidney disease on dialysis

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 210 mg of iron (equivalent to 1 g ferric citrate)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

## Chemistry Review Data Sheet

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

\_\_\_\_\_ SPOTS product – Form Completed

  X   Not a SPOTS product

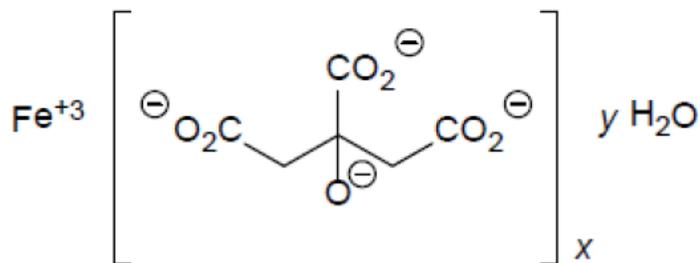
## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Names: Iron (+3), x (1,2,3-propanetricarboxylic acid, 2-hydroxy-), y (H<sub>2</sub>O)

US Adopted Name (USAN): ferric citrate

Laboratory Code: KRX-0502 and ferric citrate coordination complex

Structural Formula:



Molecular Formula: Fe • x (C<sub>6</sub>H<sub>4</sub>O<sub>7</sub>) • y H<sub>2</sub>O; x = 0.70 – 0.87, y = 1.9 – 3.3

Molecular Weight: 244.94 g/mol (based on anhydrous formula FeC<sub>6</sub>H<sub>5</sub>O<sub>7</sub>)

CAS Number: 2338-05-8

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**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCE D	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED
(b) (4)	III	(b) (4)	(b) (4)	4		
	III			4		
	III			4		

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	52,868	KRX-0502

*Note:* Following the transfer of IND 52,868 to Keryx Biopharmaceuticals, Inc. in 2006, Keryx has been responsible for the CMC IND amendments and reference to DMF (b) (4) is no longer made.

## Chemistry Review Data Sheet

## 18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	----	----
EES	Acceptable	17-Dec-2013	C. Capacci-Daniel
Pharm/Tox	N/A	----	----
Biopharmaceutics	Acceptable	02-Apr-2014	E. Chikhale
LNC			
Methods Validation			
DMEPA	'Zerenex' Not Acceptable	18-Jul-2014	J. Olumba
EA	Categorical Exclusion: Acceptable	See Review Date Above	T. Wong
Microbiology	Acceptable	09-Aug-2013	S. Langille

# The Chemistry Review for 205874

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The new drug application (205874) is recommended for **APPROVAL** from the perspective of chemistry, manufacturing, and controls.

The Office of Compliance has given an acceptable recommendation for the manufacturing and testing facilities (see Establishment Evaluation Summary at the end of CMC Review #1 – M. Cooper and T. Wong, 31-Mar-2014).

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

There are no Phase 4 commitments.

Note that the dissolution results of two out of three registration batches significantly failed the dissolution acceptance criteria at the 24-month stability time point. In the future, if a request for a shelf-life extension for the tablets beyond 18 months is received, the request should be submitted as an amendment, not an annual report.

### II. Summary of Chemistry Assessments

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

BRANDNAME (ferric citrate) Tablets (210 mg) are proposed as a medication for the control of serum phosphorus levels (b) (4) in patients with chronic kidney disease (CKD) on dialysis.

#### Drug Substance

The NDA applicant claims that ferric citrate is a coordination complex (b) (4)

(b) (4) It is unclear if these (b) (4) and no data have (b) (4) been provided to demonstrate that these are the (b) (4) responsible for the proposed (b) (4) mechanism of action. The drug substance is an (b) (4)

Ferric citrate is (b) (4)

The (b) (4) of ferric citrate drug

## Executive Summary Section

substance was found to be (b) (4)  
(b) (4) Two facilities (b) (4)  
(b) (4) manufacture the drug substance. Ferric  
citrate is packaged (b) (4)  
(b) (4) and stored (b) (4)

The applicant requested (b) (4) status for KRX-0502 (ferric citrate)  
because the drug is proposed to (b) (4)  
However, the drug substance (b) (4)  
(b) (4) It appears that it is the (b) (4)  
(b) (4)  
Therefore, the CMC reviewers recommended that the (b) (4) status be rejected (b) (4)

The drug substance manufacturing process was (b) (4)  
(b) (4). Eleven drug substance stability batches were  
manufactured using the (b) (4). The applicant proposed a drug  
substance retest date of (b) (4) months. However, based on the stability data from the 11 batches,  
a (b) (4) **month retest date is granted for the drug substance stored in the** (b) (4)

### Drug Product

The product is an immediate release film-coated, peach-colored and oval-shaped tablets for oral administration. Each tablet is debossed with "KX52" (b) (4). The proposed trade name for ferric citrate tablets, Zerenex was rejected by DMEPA. Each tablet contains 210 mg of ferric iron equivalent to 1,000 mg of ferric citrate and the following excipients: pregelatinized starch and calcium stearate. In addition, the film coating contains the following inactive ingredients: hypromellose, titanium dioxide, triacetin, and FD&C Yellow #6/Sunset Yellow FCF Aluminum Lake, FD&C Red #40/Allura Red AC Aluminum Lake, and FD&C Blue #2/Indigo Carmine Aluminum Lake. The tablets will be manufactured at (b) (4) a contract manufacturer, with proposed commercial batch size of (b) (4). The tablets are packaged in (b) (4) (b) (4) high density polyethylene (HDPE) bottles with (b) (4) in 200 tablet-count. The filled bottles are (b) (4) and capped (b) (4).  
Tablets are stored at **20 to 25°C (68 to 77°F): excursions permitted to 15° to 30°C (59°F to 86°F)**. Protect from moisture. Based on the available 24 months stability data, the applicant proposed a shelf-life of 18 months for the tablets. The available 24 months registration stability batches data showed that two out of three batches failed dissolution acceptance criterion at the 24-month time point with the third batch barely meeting the acceptance criterion at the 24-month time point. **An eighteen (18) month shelf-life is granted for tablets packaged in the proposed commercial package and stored under the aforementioned storage conditions.**

## Executive Summary Section

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

BRANDNAME (ferric citrate) tablets are indicated for the control of serum phosphorus levels. The starting dose is (b) (4) 2 tablets orally 3 times per day with meals. The dose of BRANDNAME can be increased or decreased by 1 to 2 tablets per day (b) (4) up to a maximum dose of 12 tablets daily.

**C. Basis for Approvability or Not-Approval Recommendation**

Adequate information has been provided to allow a satisfactory evaluation of the quality of both drug substance (DS) and drug product (DP). DS and DP are manufactured and packaged in accordance with the procedures and proposed specifications to assure their quality throughout shelf life. This second review cycle was necessary to confirm that a consistent amount of ferric iron is present in each tablet to ensure consistent product quality as well as patient safety and efficacy. From a CMC perspective, NDA 205874 for BRANDNAME Tablets can be approved.

Labeling negotiations have not concluded. Recommendations will continue to be routed through the clinical PM with concurrence from DMEPA.

**III. Administrative****A. Reviewers' Signatures**

See DARRTS.

**B. Endorsement Block**

Drug Substance Reviewer:	Monica D. Cooper, Ph.D.
Drug Product Reviewer:	Thomas Wong, Ph.D.
CMC Lead:	Kasturi Srinivasachar, Ph.D.
Branch Chief:	Olen Stephens, Ph.D.
Project Manager (ONDQA):	Yvonne Knight
Project Manager (OND):	Russell Fortney

**C. CC Block**

Original NDA 205874

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MONICA D COOPER

07/29/2014

For Review of the Drug Substance

THOMAS M WONG

07/29/2014

Thomas Wong reviewed the drug product portion of the application.

OLEN M STEPHENS

07/29/2014

# **NDA 205874**

## **ZERENEX (ferric citrate) Tablets**

**Keryx Biopharmaceuticals Inc.**

**Monica D. Cooper, Ph.D. (Drug Substance)  
Thomas Wong, Ph.D. (Drug Product)**

**Office of New Drug Quality Assessment  
(DNDQA1/Branch1)**

**Reviewed for the Division of Cardiovascular and Renal  
Products (HFD-110)**

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# Chemistry Review Data Sheet

1. NDA 205874
2. REVIEW #: 1
3. REVIEW DATE: 31-Mar-2014
4. REVIEWERS: Monica D. Cooper, Ph.D. (Drug Substance) and Thomas Wong, Ph.D. (Drug Product)
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA 205874	07-Aug-2013
Amendment (revised list of establishments)	21-Aug-2013
Amendment (response to 74-day letter CMC questions)	04-Nov-2013
Amendment (USAN update)	14-Feb-2014
Amendment (response to IR letter CMC questions)	04-Mar-2014
Amendment (response to IR letter Biopharmaceuticals questions)	21-Mar-2014

7. NAME & ADDRESS OF APPLICANT:

<b>Name</b>	Keryx Biopharmaceuticals Inc.
<b>Address</b>	750 Lexington Ave. 20 <sup>th</sup> Fl. New York, NY 10022
<b>Representative</b>	James Oliviero, Chief Financial Officer
<b>Telephone</b>	212-531-5970
<b>Fax</b>	212-531-5961
<b>E-Mail</b>	joliviero@keryx.com

## Chemistry Review Data Sheet

## 8. DRUG PRODUCT NAME/CODE/TYPE:

<b>Proprietary Name</b>	Zerenex
<b>Non-Proprietary Name (USAN)</b>	Ferric citrate
<b>Code Names</b>	Ferric citrate coordination complex KRX-0502
<b>Chemistry Type</b>	2
<b>Submission Priority</b>	S

## 9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

## 10. PHARMACOL. CAT./INDICATION: Iron-containing oral phosphate binder/Control of serum phosphate levels (b) (4) in patients with chronic kidney disease on dialysis

## 11. DOSAGE FORM: Tablet

## 12. STRENGTH/POTENCY: 210 mg of iron (equivalent to (b) (4) mg ferric citrate)

## 13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed Not a SPOTS product

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

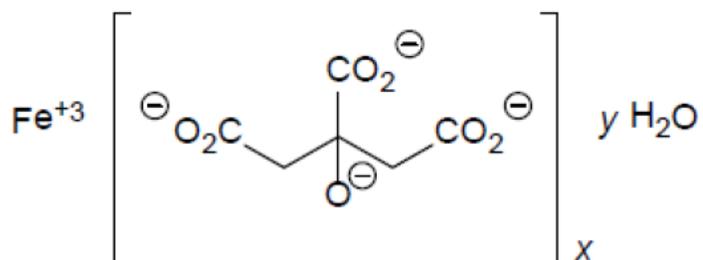
Chemical Names: Iron (+3), x (1,2,3-propanetricarboxylic acid, 2-hydroxy-), y (H<sub>2</sub>O)

US Adopted Name (USAN): ferric citrate

## Chemistry Review Data Sheet

Laboratory Code: KRX-0502 and ferric citrate coordination complex

Structural Formula:



Molecular Formula:  $\text{Fe} \cdot x (\text{C}_6\text{H}_4\text{O}_7) \cdot y \text{H}_2\text{O}$ ;  $x = 0.70 - 0.87$ ,  $y = 1.9 - 3.3$

Molecular Weight: 244.94 g/mol (based on anhydrous formula  $\text{FeC}_6\text{H}_5\text{O}_7$ )

CAS Number: 2338-05-8

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCE D	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED
(b) (4)	III	(b) (4)	(b) (4)	4		
	III			4		
	III			4		

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

Chemistry Review Data Sheet

- 2 – Type 1 DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	52,868	KRX-0502

*Note:* Following the transfer of IND 52,868 to Keryx Biopharmaceuticals, Inc. in 2006, Keryx has been responsible for the CMC IND amendments and reference to DMF (b)(4) is no longer made.

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	----	----
EES	Acceptable	17-Dec-2013	C. Capacci-Daniel
Pharm/Tox	N/A	----	----
Biopharmaceutics	Pending		E. Chikhale
LNC			
Methods Validation			
DMEPA	'Zerenex' Acceptable	07-Feb-2014	J. Olumba
EA	Categorical Exclusion: Acceptable	See Review Date Above	T. Wong
Microbiology	Acceptable	09-Aug-2013	S. Langille

# The Chemistry Review for 205874

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The new drug application (205874) is recommended for a *complete response action* from the perspective of chemistry, manufacturing, and controls due to several issues noted in Section II. C. below. The main quality concern is that the drug substance is not well-controlled, leading to significantly variable drug substance batches.

The Office of Compliance has given an acceptable recommendation for the manufacturing and testing facilities (see Establishment Evaluation Summary at the end of this review).

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

There are no Phase 4 commitments.

Note that the dissolution results of two out of three registration batches significantly failed the dissolution acceptance criteria. In the future, if a request for shelf-life extension for the tablets is received, the request should be submitted as an amendment, not an annual report.

### II. Summary of Chemistry Assessments

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

ZERENEX (ferric citrate) Tablets (210 mg) are proposed as a medication for the control of serum phosphorus levels and increase in (b) (4) patients with chronic kidney disease (CKD) on dialysis.

#### Drug Substance

The NDA applicant claims that ferric citrate is a coordination complex (b) (4)

(b) (4) It is unclear if this is (b) (4) and no data has been provided to demonstrate that these are the (b) (4) responsible for the proposed mechanism of action. The drug substance is an (b) (4)

Ferric citrate is (b) (4)

The (b) (4) of ferric citrate drug

## Executive Summary Section

substance was found to be (b) (4)  
Two facilities (b) (4)  
manufacture the drug substance. Ferric citrate is packaged in (b) (4)  
A drug substance retest date cannot be given at this time, because stability batches failed the release specification for citrate concentration and subsequent time points. It should be noted that validation and registration batches failed this specification both at the higher and lower limits, indicating the variability between batches with regards to (b) (4)  
In addition, the citrate-related impurity method (b) (4) has not been demonstrated to be stability-indicating.

The applicant requested (b) (4) status for KRX-0502 (ferric citrate) because the drug is proposed to exist as a (b) (4)  
However, the drug substance (b) (4)  
Therefore, it appears that (b) (4)

Drug Product

The applicant has developed an immediate release film-coated, peach-colored and oval-shaped tablets for oral administration. Each tablet is debossed with "KX52" (b) (4). The proposed trade name for ferric citrate tablets is Zerenex. Each tablet contains 210 mg of ferric iron equivalent to (b) (4) mg of ferric citrate and the following excipients: pregelatinized starch and calcium stearate. In addition, the film coating contains the following inactive ingredients: hypromellose, titanium dioxide, triacetin, and FD&C Yellow #6/Sunset Yellow FCF Aluminum Lake, FD&C Red #40/Allura Red AC Aluminum Lake, and FD&C Blue #2/Indigo Carmine Aluminum Lake. The tablets will be manufactured at (b) (4) a contract manufacturer, with proposed commercial batch size of (b) (4). The tablets are packaged in (b) (4) high density polyethylene (HDPE) bottles with (b) (4) in 200 tablet-count. The filled bottles are (b) (4) and capped (b) (4). Tablets are stored at 20 to 25°C (68 to 77°F): excursions permitted to 15° to 30°C (59°F to 86°F). Protect from moisture. Based on the available 24 months stability data, the applicant proposed a shelf-life of 24 months for the tablets when packaged in the proposed commercial packages and stored in the afore-mentioned storage conditions. However, the available 24 months stability data showed that two of the three batches failed dissolution acceptance criterion at the 24 months' time point with the third batch barely meeting the acceptance criterion at the 24 months' time point. **An eighteen (18) month shelf-life may be granted (when the product is approved) for tablets packaged in the proposed commercial package and stored under the afore-mentioned storage conditions.**

## Executive Summary Section

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

Zerenex (ferric citrate) tablets are indicated for the control of serum phosphorus levels. The starting dose is (b) (4) tablets orally 3 times per day with meal. The dose of Zerenex can be increased or decreased by 1 to 2 tablets per day (b) (4) up to a maximum dose of 12 tablets daily.

**C. Basis for Approvability or Not-Approval Recommendation**

NDA 205874 is recommended for a complete response action from the perspective of chemistry, manufacturing, and controls due to several issues that are noted below.

The ferric citrate drug substance is not adequately controlled, which leads to significant variability in the drug substance batches (b) (4)

The current control strategy and manufacturing process (b) (4) Since the mechanism of action is thought to be dependent on ferric ion concentration, the drug product should be formulated based on the ferric concentration in the drug substance. (b) (4)

Furthermore, the citrate-related impurity method has not been shown to be stability-indicating, so it cannot be used to determine a retest date or control release of the drug substance for drug product manufacturing. Out-of-specification results were observed for (b) (4) specification (b) (4) during stability studies and at the initial stability time point. Therefore, a retest date cannot be determined for the ferric citrate drug substance. Tighter controls of the ferric iron and citrate concentrations must be implemented before an 'approval' recommendation is rendered from CMC.

Labeling negotiations have not concluded as the applicant has not agreed to the strength presentation of their product. Recommendations will continue to be routed through the clinical PM with concurrence of DMEPA.

A draft discipline review letter is appended to the end of this review.

**III. Administrative****A. Reviewers' Signatures**

See DARRTS.

## Executive Summary Section

**B. Endorsement Block**

Drug Substance Reviewer:	Monica D. Cooper, Ph.D.
Drug Product Reviewer:	Thomas Wong, Ph.D.
CMC Lead:	Kasturi Srinivasachar, Ph.D.
Branch Chief:	Olen Stephens, Ph.D.
Project Manager (ONDQA):	Yvonne Knight
Project Manager (OND):	Russell Fortney

**C. CC Block**

Original NDA 205874

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MONICA D COOPER  
03/31/2014

THOMAS M WONG  
03/31/2014

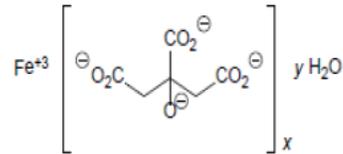
OLEN M STEPHENS  
03/31/2014

CMC Recommendation is for a complete response action. A draft list of deficiency comments are attached to the end of the review.

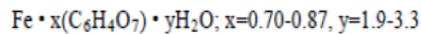
Initial Quality Assessment  
Branch I

**OND Division:** Division of Cardiovascular and Renal Products  
**NDA:** 205874  
**Applicant:** Keryx Biopharmaceuticals, Inc.  
**Letter Date:** Aug 7, 2013  
**Stamp Date:** Aug 7, 2013  
**PDUFA Date:** June 7, 2014 (Standard Review)  
**Tradename:** (b)(4) (proposed)  
**Established Name:** Ferric citrate coordination complex (USAN?)  
**Dosage Form:** Tablet, 1g  
**Route of Administration:** Oral  
**Indication:** Control of serum phosphate levels and increase in (b)(4)  
(b)(4) patients with chronic kidney disease on dialysis  
**Assessed by:** Kasturi Srinivasachar  
**ONDQA Fileability:** Yes

**Chemical Structure**



**Chemical Formula**



**Formula Weight**

The formula weight for the anhydrous formula  $\text{FeC}_6\text{H}_5\text{O}_7$  is 244.94 g/mole.

## Summary

This is an e-CTD 505(b)(2) NDA for a new phosphate binder, ferric citrate, with the code name KRX-0502. This is formulated into 1 g (b)(4) each containing about 210 mg iron. The drug is indicated for the control of serum phosphorus levels in patients with chronic kidney disease who are on dialysis. Upon oral administration with a meal, phosphate binding takes place in the GI tract by dissociation of the ferric ion from citrate and formation of insoluble ferric phosphate which is then excreted. (b)(4)

KRX-0502 was developed under IND 52,868 and the NDA was submitted via the 505(b)(2) regulatory pathway because the applicant is referencing the published literature for data from non-clinical reproductive toxicology, carcinogenicity and mutagenicity studies.

There were two meetings with the firm where CMC topics were discussed, a CMC specific EOP2 meeting on Feb. 24, 2010 and a pre-NDA meeting held on Aug. 13, 2012. The EOP2 meeting was mainly focused on the adequacy of the drug substance and drug product specifications. The Applicant was advised to consider (b)(4) an impurity and include it in the drug substance and drug product specifications with appropriate test methods and acceptance criteria. They were also recommended to justify the choice of (b)(4) impurities for inclusion in the drug substance specification as well as the acceptance criteria. Non-clinical and CMC disciplines were involved in the pre-NDA meeting where the issue of the impurity, (b)(4) was brought up again. Keryx stated that they were encountering difficulties in developing a (b)(4) method that uses a (b)(4)

This was not acceptable to the Agency and Keryx was told to use the method they already had developed to generate preliminary data on levels of this impurity. Since two contract manufacturers were proposed for the drug substance, Keryx was reminded that drug product registration batches should be manufactured using at least one lot of drug substance from each of the contract sites. Other issues discussed were specification limits for (b)(4) impurities in the drug substance and the adequacy of the toxicity studies used to qualify citrate related impurities. The Applicant has claimed a (b)(4)

This claim has been (b)(4) denied by the Agency

## Drug Substance

Ferric citrate is a (b)(4)

The structure of ferric citrate has been

(b) (4)

The specification includes identification and assay tests for ferric ion, citrate identification and content, citrate related impurities, (b) (4), ferrous and (b) (4) content, (b) (4) (b) (4) impurities, particle size distribution, (b) (4) and microbial limits. A (b) (4) method is used for assay of (b) (4) whereas citrate content and citrate related impurities are determined by (b) (4) (b) (4) is used for quantitation of all (b) (4) impurities except (b) (4) which is determined by (b) (4) Batch analysis data have been submitted for toxicology, clinical and validation/commercial batches ranging in size from (b) (4) Kg to (b) (4) Kg.

Stability data have been provided for 10 batches of drug substance – 9 batches from the (b) (4) process and 1 batch from (b) (4) 36 months of data are available for two of the batches ( (b) (4) 24 and 12 months' data are provided for 1 batch each from (b) (4) and 6 months of long term data have been submitted for the remaining batches. Accelerated testing has been completed for all 10 batches. The Applicant states that real time and accelerated stability studies have also been initiated for 1 pre-validation and 3 validation batches manufactured at (b) (4) The tests performed include appearance, ferric iron assay, citrate content, ferrous iron content, impurities/degradants, (b) (4) and microbial limits. It is claimed that a retest period of at least (b) (4) months is supported by the data generated.

### Drug Product

The drug product is a film-coated, peach colored and oval shaped immediate release (b) (4) containing 1 g (actually (b) (4) mg) of ferric citrate. The (b) (4) contains (b) (4) excipients, pre-gelatinized starch NF and calcium stearate NF. (b) (4) ferric citrate (b) (4) It is a mixture of compendial excipients and FD&C colors. The unit dosage composition of the drug product is given in terms of a target quantity and a range for ferric citrate and the excipients. Potential critical quality attributes of the drug substance that were considered to meet the target drug product profile include (b) (4) form, particle size, surface area, assay, process impurities and (b) (4). The key challenges to the development of ferric citrate (b) (4) and the design strategy employed during development to mitigate any adverse impact on the target product profile have been identified. Given the high therapeutic dosage and (b) (4) dissolution desired, a (b) (4) mg (b) (4) manufactured (b) (4) Initial Phase 3 trials used 1 g

caplets with (b) (4) % w/w (b) (4) as (b) (4) but later Phase 3 clinical and manufacturing process validation studies employed 1 g caplets with (b) (4) % (b) (4)

Based on the formulation development work, pilot scale (b) (4) Kg) batches were manufactured and further studies were initiated to develop a manufacturing process for a commercial dosage form with appropriate quality attributes. This involved the manufacturing process risk assessment of a number of factors like (b) (4) to the proposed commercial scale of (b) (4) kg.

The manufacturing process for commercial product consists of (b) (4)

Specifications for the product include the standard test attributes of appearance, identification (ferric salts and citrate), assay for ferric iron and citrate content, citrate related impurities/ degradants, (b) (4), uniformity of dosage units, dissolution, (b) (4) and microbial limits. Ferric iron assay and (b) (4) are determined by (b) (4) methods (b) (4) which are similar to the ones for the drug substance.

Citrate content and citrate related impurities are quantitated by (b) (4). Batch analysis data have been submitted for clinical, registration/stability and commercial scale batches.

Stability of the drug product has been monitored on 3 primary commercial scale batches at long term and accelerated storage conditions. The drug substance used in these batches were manufactured by (b) (4). 18 months' long term data are available on two of the batches and 12 months' data have been submitted for the third batch. The accelerated studies at 40°C/75%RH were carried out on one batch for 6 months but discontinued after 3 months for the other two batches because of dissolution failures. Supportive stability data from batches

(b) (4) and (b) (4) have also been submitted. One of these supportive batches was manufactured from (b) (4) drug substance and all the others utilized (b) (4) ferric citrate. Photostability testing was carried out on one lot of ferric citrate bulk tablets in accordance with ICH Q1B, Option 2 and it is claimed that the data indicate light does not significantly affect the properties of the product. The Applicant also states that the source of drug substance and the level of (b) (4) in the formulation (in the range (b) (4) % to (b) (4) %) do not affect product stability. The (b) (4)

A (b) (4) month shelf-life is proposed for ferric citrate tablets.

## Critical Review Issues Drug Substance

- Has the structure of the drug substance been conclusively established, in particular, the proposed (b) (4) coordination complexes? Is (b) (4) reliable for determining that the (b) (4) complex is the (b) (4), as claimed? Have various batches of drug substance been analyzed to show that the (b) (4) complexes is reasonably constant? Does any of this matter or is the phosphate binding solely determined by the concentration of soluble ferric iron in solution?
- Is the manufacturing process used by both suppliers described in sufficient detail with adequate in-process controls? Will both (b) (4) be used at (b) (4) for commercial batches?
- Are the physical properties and impurity profiles of drug substance from both suppliers equivalent?
- Has a justification been provided for the choice of (b) (4) impurities that are controlled in the starting material, (b) (4), and the drug substance?
- It is stated that future batches of drug substance will employ (b) (4). Is this switch acceptable and will the specification remain the same? A similar switch proposed for (b) (4) should also be evaluated.
- Regarding the specification:
  - Is it justified to have (b) (4) for all (b) (4) impurities as compared to the starting material. (b) (4)?
  - The Applicant has not included a test for (b) (4) but claims to have established a limit of (b) (4) % w/w using the current (b) (4) method. They propose to (b) (4). Is this acceptable?
  - Does the assay test for ferric iron include the ferric content from the impurity, (b) (4)?
  - Is a D90 limit sufficient for particle size distribution?
- Should the impurity (b) (4) be monitored in the stability studies?
- Is the proposed retest date of (b) (4) months acceptable?

### Drug Product

- The strength of the (b) (4) is given as 1 g even though the unit dose formulation contains (b) (4) mg of ferric citrate. Is this rounding up acceptable?
- In Sections 2.3.P.1.2 and 3.2.P.1.2 under Composition ranges have been listed for ferric citrate and the excipients. It is not clear whether these ranges imply that the Applicant desires (b) (4). This needs to be clarified.
- Is the manufacturing process described in sufficient detail with appropriate in-process controls and is it consistent with the executed batch records provided in 3.2R?
- Has it been established that (b) (4) is solely a drug substance (b) (4) impurity since it is not included in the product specification?
- Evaluation of the dissolution method and acceptance criteria is the responsibility of the Biopharm reviewer who should also take into consideration the dissolution failures observed at accelerated and intermediate stability storage conditions.
- Regarding stability:
  - Is the shelf-life proposed by the Applicant ((b) (4) months) reasonable given the dissolution failures at accelerated and intermediate storage conditions? In

addition, 18 months' long term data are available for 2 primary batches and only 12 months' data on the third batch.

- The Applicant ascribes the dissolution failures (b) (4)  
Is there any evidence for this? The effect should be (b) (4)
- None of the primary stability batches utilize drug substance from (b) (4) –3 months' data from only one supportive batch which is manufactured using (b) (4) drug substance are provided. Is this sufficient? Should the post-approval commitment protocol for the first 3 commercial batches include product from both drug substance sites?

### Labeling

- The Applicant claims that USAN has accepted the established name (b) (4) however, this name is not in the current USAN dictionary. This claim should be verified. If the correct USAN name is “ferric citrate” all labeling will have to be revised accordingly.
- (b) (4) is not recognized by USP as an official solid oral dosage form designation. This should be changed to “tablet”
- The strength “1g” is not technically correct since each tablet contains (b) (4) mg of ferric citrate
- Can the excursion provision in the storage statement be allowed given the dissolution failure (b) (4)?
- In the Description section of the PI (b) (4) should be replaced with its constituent ingredients.

### Comments and Recommendations

The application is fileable -- see attached Filing Check List. Facilities will be entered into EES shortly; the reviewer should confirm the completeness and accuracy of the entries. The microbiology reviewer has filed a review stating that the application can be approved from the product quality microbiology perspective. A categorical exclusion from environmental assessment has been requested. Methods validation will be not be initiated at this time since this is not an NME. However, the reviewer should evaluate the non-traditional methods used for the drug substance and drug product to see if methods validation is called for. This NDA has been selected for the Integrated Product and Process/Facility Pilot program and will have a 3 person review team consisting of drug substance, drug product and process reviewers.

Kasturi Srinivasachar  
CMC Lead

Aug. 29, 2013  
Date

Ramesh Sood  
Branch Chief

Aug. 29, 2013  
Date

PRODUCT QUALITY -- CMC and BIOPHARMACEUTICS  
FILING REVIEW FOR NDA

**NDA Number:** 205874      **NDA Type:** 2      **Established/Proper Name:** Ferric citrate (b) (4)  
(not confirmed with USAN) (u) (u)

**Applicant:** Keryx Biopharmaceuticals      **Letter Date:** Aug 7, 2013      **PDUFA Goal:** June 7, 2014 (Standard Review)  
**Stamp Date:** Aug 7, 2013

**CMC Reviewers:** Monica Cooper, Thomas Wong and Vibhakar Shah

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

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

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		Revised 356h submitted with additional facilities
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>			NA

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		

10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		
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\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Categorical exclusion requested

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

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

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

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			NA

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

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

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	<b>IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?</b>	X		Fileable for Product Quality. See Biopharmaceutics Filing Review for fileability of the Biopharm Section
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			NA
36.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			See Biopharm Filing review
37.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?	X		Confirmation of USAN name if this cannot be done internally

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KASTURI SRINIVASACHAR  
08/29/2013

RAMESH K SOOD  
08/30/2013