CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205874Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 205874	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Zerenex Established/Proper Name: ferric citrate Dosage Form: tablet Strengths: (b) (4) mg ferric citrate (contains 210 mg ferric iron)		
Applicant: Keryx Biopharmaceuticals		
Date of Receipt: 8/7/13		
PDUFA Goal Date: 6/7/14	Action Goal Date (if different):	
RPM: Russell Fortney		
Proposed Indication(s): control of serum phosphorous levels in patients with CKD		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Published literature	**Oral reproductive toxicity, genotoxicity, oral carcinogenicity. The sponsor also referenced literature information regarding pharmacology, absorption, distribution and acute toxicity.**

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Keryx Biopharmaceuticals' ferric citrate coordination complex relies on published literature to support nonclinical reproductive toxicology, carcinogenicity, and mutagenicity studies. The rationale for reliance on the nonclinical safety established in the published literature is that the bioavailability of ferric salts (of which ferric citrate coordination complex is), when administered orally, is generally low and, as a PO4 binder, the bioavailability can be expected to be even lower (orally administered ferric citrate reacts with PO4 in the GI tract, precipitating PO4 as ferric phosphate). The latter is insoluble and is excreted in the stool, reducing the amount of phosphate (and iron) that is absorbed from the GI tract. Since the levels of ferric citrate absorbed (and therefore available in the systemic circulation) is expected to be lower with this product than the levels in the published literature, the finding of nonclinical safety supported by the published literature is supportive of the nonclinical safety of this product.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☒

NOTE: one literature report refers to JTT-751, which is chemical name of the sponsor's product in their Japanese applications.

*If "**NO**", proceed to question #5.*
*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☐ NO ☒

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*
*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:
   a) Approved in a 505(b)(2) application?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

   b) Approved by the DESI process?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

   c) Described in a final OTC drug monograph?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

   d) Discontinued from marketing?

YES ☐ NO ☐

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

      i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

NOTE: Several ferric-iron containing products are approved, either for the same indication (reduction of serum phosphorous) or as an iron replacement therapy.

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☐ NO ☒

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternatives:
NDA 203565 Injectafer
NDA 20955 Ferrlicit
NDA 205109 Velphoro

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):
No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☒ No patent certifications are required (e.g., because application is based solely on

published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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/s/

RUSSELL FORTNEY
09/03/2014

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: August 15, 2014

To: Russell Fortney
Regulatory Project Manager
Division of Cardiology and Renal Products (DCRP)

From: Puja Shah, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Zarna Patel, PharmD
Regulatory Review Officer, OPDP

Subject: NDA 205874
ZERENEX® (ferric citrate) Tablet containing 210 mg of ferric iron equivalent to 1 g ferric citrate for Oral Use

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Background

This consult review is in response to DCRP's October 29, 2013, request for OPDP's review of the draft package insert (PI) for ZERENEX® (ferric citrate) Tablet containing 210 mg of ferric iron equivalent to 1 g ferric citrate for Oral Use. OPDP reviewed the substantially complete version of the draft PI provided by the Division of Medical Policy Programs (DMPP) on August 4, 2014. Our comments on the PI are included directly on the attached copy of the labeling.

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Puja Shah at 240-402-5040 or puja.shah@fda.hhs.gov

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

PUJA J SHAH
08/15/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Final Label and Labeling Memorandum

Date:	May 22, 2014
Reviewer:	Jean Olumba, MD, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Lisa Khosla, PharmD, MHA Division of Medication Error Prevention and Analysis
Drug Name and Strengths:	Zerenex (ferric citrate) tablet 210 mg of ferric iron equivalent to (b) (4) mg of ferric citrate
Application Type/Number:	NDA 205874
Applicant:	Keryx Biopharmaceuticals, Inc.
OSE RCM #:	2013-1856-1

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This memorandum evaluates the revised labels and labeling for Zerenex (ferric citrate) tablet , submitted on May 20, 2014 (Appendix A). DMEPA previously reviewed the proposed labels and labeling under OSE Review# 2013-1856, dated May 12, 2014.

2 MATERIAL REVIEWED

DMEPA reviewed the labels and labeling submitted on May 20, 2014. We compared the revised labels and labeling against the recommendations contained in OSE Review# 2013-1856 dated May 12, 2014.

3 CONCLUSIONS AND RECOMMENDATIONS

The revised labels adequately address our concerns from a medication error perspective. We have no additional comments at this time.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager: Karen Bengtson at 301-796-3338.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JEAN C OLUMBA
05/22/2014

LISA V KHOSLA
05/22/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 14, 2014
Requesting Office or Division:	Office of New Drug Quality Assessment (ONDQA)
Application Type and Number:	NDA 205874
Product Name and Strength:	Zerenex (ferric citrate) tablets (b) (4) mg
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Keryx Biopharmaceuticals, Inc.
Submission Date:	November 04, 2013 and April 11, 2014
OSE RCM #:	2013-1856
DMEPA Primary Reviewer:	Jean Olumba, MD, PharmD.
DMEPA Team Leader:	Lisa Khosla, PharmD, MHA

1. REASON FOR REVIEW

This review is in response to a request from the Office of New Drug Quality Assessment (ONDQA) to evaluate the proposed 200 –count trade container label and carton labeling for Zerenex (Ferric Citrate) tablets from a medication error perspective.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B (N/A)
ISMP Newsletters	C (N/A)
Previous DMEPA Reviews	D (N/A)
Regulatory History	E (N/A)
• 200-count Trade Container Label • 200-count Trade Carton Labeling • Insert Labeling	F

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Zerenex (ferric citrate) is a new molecular entity that proposes to provide more options for the (b) (4) of phosphorus (b) (4) levels in chronic kidney disease patients on dialysis. We reviewed the labels and labeling associated with Zerenex and note that container label and carton labeling present the proprietary name in all capital letters. We also note that the presentation of the established name is less than ½ the proprietary name and lacks

prominence. We also note that the presentation of the NDC number appears abbreviated and does not follow the customary sequence. In addition, the presentation of the net quantity is in close proximity with the strength presentation and has equal prominence with the strength presentation, which may increase confusion. Additionally, the container label and carton labeling lacks the statement of dosage. Furthermore, the net quantity appears on the back of the carton labeling which lacks prominence. Therefore, we provide recommendations in Section 4 to address these issues.

4. CONCLUSIONS RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase clarity, to promote the safe use of the product, and to mitigate any confusion.

4.1 RECOMMENDATIONS FOR THE APPLICANT

A. Trade container label

1. Revise the presentation of the proprietary name from all caps (i.e. BRAND) to title case (i.e. Brand) to improve readability of the name. Words set in title case are easier to read than the rectangular shape that is formed by words set in all capital letters.
2. Ensure the established name is at least ½ the size of the proprietary name, and commensurate in prominence with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printing factors in accordance with 21 CFR 201.10(g)(2).
3. Add the statement of dosage in accordance with 21 CFR 201.55.
4. As currently presented, the NDC number is abbreviated as '59922' which does not appropriately identify the product. Since the NDC number is often used as an additional verification prior to drug dispensing in the pharmacy, it is an important safety feature and should be presented in accordance with 21 CFR 207.35(3)(i).
5. Unbold and relocate the net quantity statement ("200 tablets") away from the product strength. Consider placing the net quantity statement toward the bottom of the principal display panel (PDP). Post-marketing reports have shown that the net quantity and strength can be confused when they are in close proximity to each other.

B. Trade carton labeling

1. See comments A.1. through A.4.
2. As currently presented, the net quantity statement '200 tablets' is located on the back panel. Relocate the net quantity statement ("200 tablets") from the back panel to the bottom of the principle display panel, away from the product strength, to increase the prominence of this important information.

4.2 RECOMMENDATIONS TO THE DIVISION

A. Insert Labeling

1. In the DOSAGE AND ADMINISTRATION section 2, it does not state that Zerenex can be chewed, crushed, or should be swallowed whole. Upon further clarification with with the Chemistry, Manufacturing, and Controls reviewer (CMC), the product should be swallowed whole. We recommend adding the statement " Swallow the tablet whole. Do not split, crush, or chew the tablet." to be consistent with intended use of Zerenex.

If you have further questions or need clarifications, please contact Karen Bengtson, OSE project manager, at 301-796-3338.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Zerenex that Keryx Biopharmaceuticals, Inc. submitted on November 04, 2013 and revised on April 11, 2014

Table 2. Relevant Product Information for Zerenex	
Active Ingredient	Ferric Citrate
Indication	Control of serum phosphorus levels (b) (4) in patients with chronic kidney disease on dialysis
Route of Administration	Oral
Dosage Form	Tablets
Strengths	(b) (4) mg
Dose and Frequency	Starting dose is (b) (4) 2 tablets orally 3 times per day with meals. The dose can be increased or decreased by 1 to 2 tablets per day at (b) (4) week intervals as needed to maintain serum phosphorus at recommended target levels (3.5 to 5.5 mg/dL), up to a maximum dose of 12 tablets daily. (b) (4)
How Supplied	200 tablets in 400-cc high-density polyethylene bottles
Storage	Store at 20 to 25°C (68 to 77°F): excursions permitted to 15° to 30°C (59°F to 86°F) [See USP controlled room temperature]. Protect from moisture.

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

N/A

B.3 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

APPENDIX C: ISMP NEWSLETTERS'

C.1 Methods

N/A

APPENDIX D. PREVIOUS DMEPA REVIEWS

D.1 Methods

N/A

APPENDIX E: REGULATORY HISTORY

N/A

APPENDIX F. CONTAINER LABEL, CARTON LABELING, INSTRUCTIONS FOR USE, MEDICATION GUIDE

F.1 List of Label and Labeling Reviewed

We reviewed the following Zerenex labels and labeling submitted by Keryx Biopharmaceuticals, Inc. on November 04, 2013 and revised on April 11, 2014.

- 200-count Trade Container Label
- 200-count Trade Carton Labeling
- Insert Labeling

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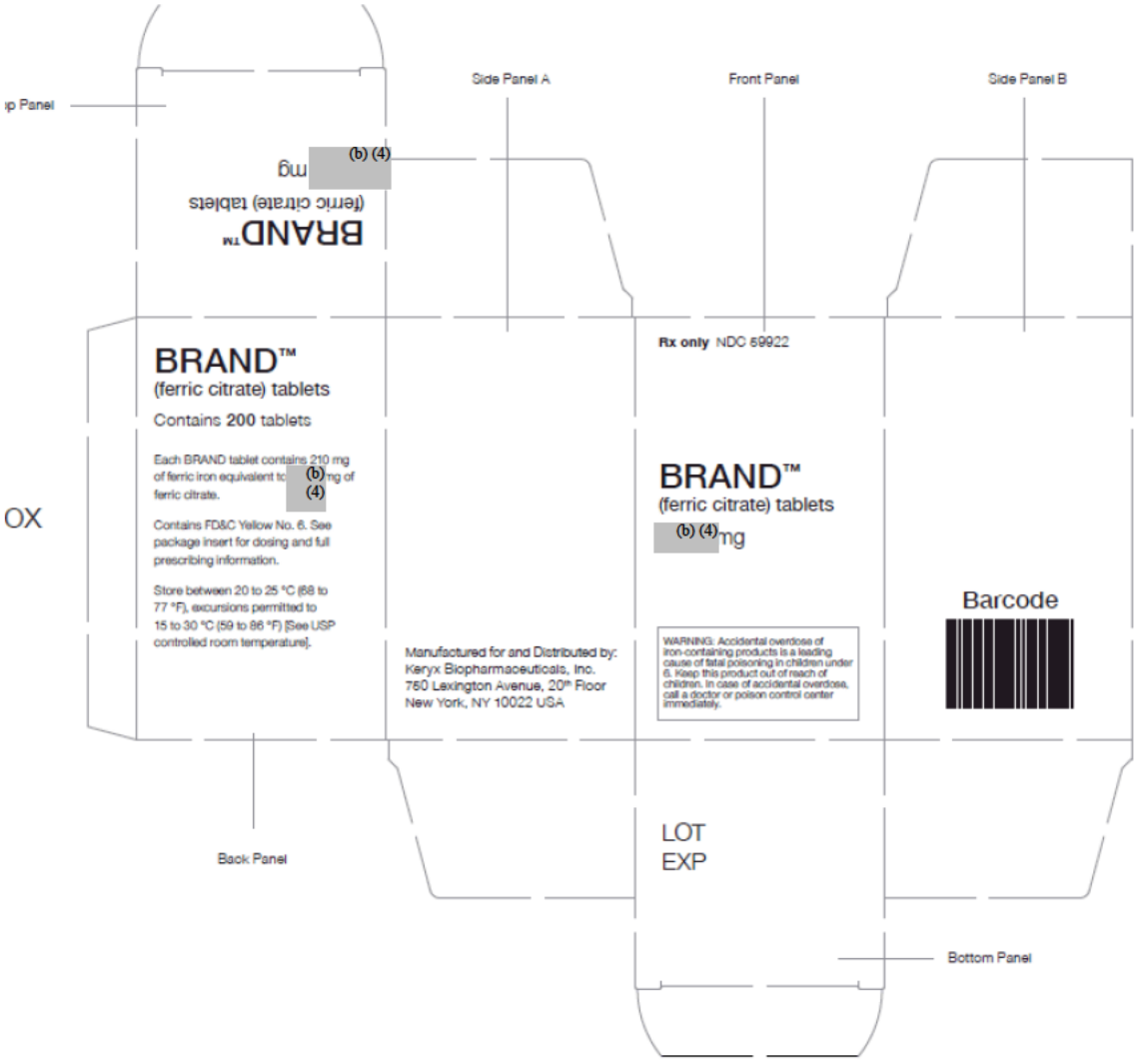
F.2 Label and Labeling Images

Trade Container Label

Trade Carton Labeling



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/s/

JEAN C OLUMBA
05/14/2014

LISA V KHOSLA
05/16/2014

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: March 31, 2014

TO: Aliza Thompson, Medical Officer Team Leader
Nancy Xu, Medical Officer
Russell Fortney, Regulatory Project Manager
Division of Cardio-Renal Drug Products

FROM: Sharon K. Gershon, Pharm. D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D.; M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 205874

APPLICANT: Keryx Biopharmaceuticals

DRUG: (b) (4) (ferric citrate)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: control of serum phosphorus levels; [redacted]

Protocols:

KRX-0502-304: A Three-Period, 58-Week Safety and Efficacy Trial of KRX- 0502 (Ferric Citrate) in Patients with End-Stage Renal Disease (ESRD) on Dialysis

KRX- 0502-305: A 4-Week Dose-Ranging and Efficacy Study of KRX- 0502 (Ferric Citrate) in Patients with End-Stage Renal Disease.

CONSULTATION REQUEST DATE: October 21, 2013

INSPECTION SUMMRY GOAL DATE: April 7, 2014

DIVISION ACTION GOAL DATE: June 7, 2014

PDUFA DATE: June 7, 2014

I. BACKGROUND:

Keryx Biopharmaceuticals, Inc. (Keryx) submitted New Drug Application 205874, ferric citrate 1-gram [redacted] (KRX-0502) for the control of serum phosphorus levels [redacted] in patients with chronic kidney disease (CKD) on dialysis.

Two clinical studies, Study KRX-0502-304 and Study KRX-0502-305, provide the primary support for the efficacy claim of KRX-0502 as a phosphate binder.

Study KRX-0502-304 was a Phase 3, multicenter, randomized, open-label, active-controlled and then placebo-controlled study in subjects with CKD on thrice-weekly dialysis. Among the 1072 subjects screened, 441 subjects were randomized at 56 study site in the U.S. and two sites in Israel. A total of 289 subjects received KRX-0502 and 149 received active control. The primary efficacy endpoint of this study was the change in serum phosphorus in the Efficacy Assessment Period (EAP) from Week-52 (baseline) to Week 56. The starting dose of KRX-0502 was 6 g/day, and subjects were titrated up to 12 g/day to maintain serum phosphorus between 3.5 and 5.5 mg/dL.

Study KRX-0502-305 was a Phase 3, multicenter, randomized, open-label, dose ranging safety and efficacy study in subjects with CKD on thrice-weekly dialysis. Subjects who met the eligibility criteria underwent a 1-to 2-week washout from all phosphate-binding agents before starting study drug. Subjects were randomized in a 1:1:1 ratio to 1 of 3 fixed doses of KRX-0502 (1, 6, or 8 g/day) and took KRX-0502 as 1-gram oral [redacted] every day for four weeks. Efficacy was assessed based on the change in concentrations of serum phosphorus, the primary endpoint, and secondary endpoints including calcium, ferritin, transferrin saturation level (TSAT) and bicarbonate. Among the 339 subjects screened, 154 subjects were randomized at 15 study sites in the U.S., and 151 subjects received KRX-0502. The primary efficacy endpoint

of this study was the change in serum phosphorus from baseline to Day 28.

Rationale for Site Selection
These sites were chosen for inspection because of large enrollment relative to other sites; high treatment responders/greater efficacy (Schulman), and a past OAI classification (Whittier). (b) (4)

A field investigator from the Cincinnati District Office was previously assigned to conduct the inspection of Dr. Whittier, at his office located in Canton, Ohio. Upon contacting the site, she learned that Dr. Whittier had retired, and that his records were sent for storage at the sponsor location. A limited inspection was conducted of Dr. Whittier's records at the sponsor site.

Name of CI/Address	**Protocol # and # of Subjects**	**Inspection Dates**	**Final Classification**
Gerald Schulman Vanderbilt University School of Medicine 215 MAB, 1211 21st Avenue South Nashville, TN 37240	KRX-0502-304 14 subjects KRX-0502-305 16 subjects Site 109	November 29 – December 13, 2013	VAI
Mark Smith 815 12th Street Augusta, GA 30909	KRX-0502-304 13 subjects KRX-0502-305 18 subjects Site 112	December 2 – 6, 2013	NAI
Frederick Whittier 4974 Higbee Ave., NW Suite 100 Canton, OH 44718	KRX-0502-304 9 subjects Site 129	January 6-9, 2014	NAI

Key to Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. Gerald Schulman
Vanderbilt University School of Medicine
215 MAB, 1211 21st Avenue South
Nashville, TN

a. What was inspected: This inspection was conducted according to Compliance Program 7348.811. Dr. Schulman has nine INDs in CDER's COMIS database, and no prior FDA inspection. The FDA field investigator reviewed the following items during the inspection: informed consent documents for all subjects in both studies; IRB approvals and correspondences; financial disclosure statements; training records; sponsor and monitor correspondences; corroboration of laboratory results for serum phosphorus, calcium, ferritin, iron, and TSAT% for all subjects at all visits for both studies; review and corroboration of all source documents and case report forms (CRFs) for all screen failures in both studies; review and corroboration of complete source document records and CRFs for six subjects in KRX-0502-305 (4-week study); partial or complete review and corroboration of source records and CRFs for all 25 subjects enrolled in KRX-0502-304 (58-week study).

For KRX-0502-304 (58-week study), the site screened 36 subjects and enrolled 25 subjects. Three subjects withdrew due to adverse events or death, one subject withdrew consent during the study, and one subject discontinued and relocated to another state.

For KRX-0502-305 (4-week study), the site screened 23 subjects, and re-screened two subjects, as permitted by the protocol. Six subjects were screen failures, and three subjects failed following the washout period. One subject withdrew due to an adverse event, and one subject was discontinued from therapy due to treatment failure.

b. General observations/commentary: For the six audited subjects for KRX-0502-304 (4-week study), the FDA field investigator reported that all adverse events reflected in the data listings were captured by source documents, and no discrepancies were noted between data listings and laboratory records with respect to serum phosphorus, serum calcium, bicarbonate, ferritin, iron and TSAT%.
At the conclusion of this inspection, no Form FDA 483 was issued. All issues identified were discussed at closeout with Dr. Schulman and his staff. However, upon review of the EIR, OSI is classifying the inspection as VAI based on the large number of protocol violations identified during the inspection. A summary of these violations along with an assessment of their significance are noted below.

For KRX-05-304 (58-week study), the FDA field investigator observed the protocol deviations of failure to identify and document two subjects as treatment failures as defined by the protocol. Specifically:

i. The protocol stated that if a subject was compliant with 12 caplets/day of ferric citrate on at least two consecutive visits, and had a serum phosphorus > 8.0

mg/dL, the subject will be considered a treatment failure. Subject SHM-018 was on the maximum of ferric citrate, 12 caplets per day for Visits 20 and 21. Laboratory results for Visits 20 and 21 reported serum phosphorus as 8.1 mg/dL and 8.5 mg/dL, respectively. The subject was not documented as a treatment failure until Visit 22 when the subject had a serum phosphorus level of 9.9 mg/dL.

OSI Reviewer Comments: OSI considers this a minor violation. The serum phosphorus levels were not significantly high at those visits, and the subject was appropriately considered a treatment failure at the next visit.

ii. The protocol stated that if a patient has an adjusted serum calcium > 10.5 mg/dL, and is in the active-control arm on calcium acetate, the PI may choose to stop the calcium acetate after consultation with the CCC. These patients were to be considered treatment failures.

Subject AET-024-013 was in the active control arm on calcium acetate. At Visit 17, laboratory testing reported serum calcium of 12.6 mg/dL. The Visit 18 CRF reported "study drug withdrawn" due to the adverse event of hypercalcemiabut did not identify the subject as a treatment failure.

OSI Reviewer Comments: OSI considers this a minor regulatory violation, and unlikely to significantly impact data integrity.

For KRX-05-304 (58-week study), the protocol stated that IV iron therapy was not permitted if the serum ferritin is > 1000 mcg/L or the TSAT is > 30%, without consulting with the CCC. If it was deemed in the patient's best interest to receive IV iron outside these parameters, the CCC should be consulted, and if approved and documented, it would be considered a protocol exception.

For the 19 subjects who participated in the safety assessment period three had reported protocol exceptions for IV iron administered with a TSAT > 30%.
The field investigator observed an additional five subjects with instances of IV iron administration while the subject's TSAT was > 30%, and without documented approval of the CCC. It was noted that whereas the iron sucrose administration was reported to the Concomitant Medication CRF, it was not reported as a protocol violation. For example:

i. Subject # (b) (6)-007: Visit 0 (6/9/2011) laboratory testing reported a TSAT of 32% . Visit 4 (6/30/2011) laboratory testing reported a TSAT of 40%. Visit 11 (9/22/2011) laboratory testing reported a TSAT of 38% on 9/28/2011. The Concomitant Medication CRF indicated that six doses of iron sucrose 100 mg. were administered in the period 6/14/2011 to 7/19/2011.
ii. Subject # (b) (6)-023: Visit 14 (2/15/2012) laboratory testing reported a TSAT of 33% on 2/18/2012. Visit 15 laboratory testing reported a TSAT of 30% on 3/16/2012. The

Concomitant Medication CRF indicated that iron sucrose 100 mg. was administered six times in the period 2/13/2012 to 3/19/2012.

iii. Subject # (b) (6)-028: Visit 15 (2/1/2012) laboratory testing reported a TSAT of 33% on 2/3/2012. During dialysis treatment on 2/13/2012, reports documented that 100 mg of iron sucrose was administered. Visit 16 (2/29/2012) laboratory testing reported a TSAT of 40% on3/2/2012. During dialysis treatment on 3/12/2012, 100 mg of Venofer (iron sucrose) was administered.

iv. Subject # (b) (6)-036: Visit 13 (1/25/2012) laboratory testing reported a TSAT of 31% on 1/27/2012. During dialysis treatments on 1/30/2012, 2/6/2012, and 2/13/2012, the subject was administered 100 mg of Venofer (iron sucrose). Visit 14 (2/22/2012) laboratory testing reported a TSAT of 42% on 2/24/2012.

v. Subject # (b) (6)-038: Visit 0 (8/31/2011) laboratory testing reported a TSAT of 34% on 9/2/2011. On 9/2/2011, the Study Coordinator sent an email alerting dialysis staff to hold IV iron unless permission was requested in advance. During dialysis treatment on 9/5/2011, 100 mg of Venofer (iron sucrose) was administered. Visit 13 (2/1/2012) laboratory testing reported a TSAT of 42% on 2/3/2012. During a dialysis treatment on 2/6/2012, 100 mg of Venofer (iron sucrose) was administered.

OSI Reviewer Comments: Dr. Schulman stated these administrations of IV iron were likely due to confusion at the dialysis clinics. He stated the dialysis clinic has its own protocol for the administration of IV iron and that many dialysis patients receive it with each visit. He also noted nurses rotate within the clinics and that technicians, not the nurses, administer the medications.

For Study KRX-0502-304 (58-Week), protocol violations were observed concerning ferric citrate dose adjustments not made in accordance with the titration schedule. For example:

i. Subject # (b) (6)-030: Visit 12 (10/27/2011) laboratory testing reported serum phosphorus of 6.9 mg/dL on 10/29/2011. According to the protocol titration schedule, if serum phosphorus is between 5.6 mg/dL and 6.9 mg/dL the ferric citrate dose should be increased by 1 caplet per day. On 11/10/2011, the Study Coordinator increased the dose of ferric citrate by 3 pills per day.

OSI Reviewer Comments: This was a minor error because the protocol required a dose adjustment of 3 pills if serum phosphorus was > 6.9 mg/dL.

ii. Subject # (b) (6)-037: Visit 18.1 (7/6/2012) laboratory testing reported serum phosphorus of 2.4 mg/dL on 7/9/2012. According to the protocol titration schedule, if serum phosphorus is < 2.5 mg/dL the ferric citrate should be held until serum phosphorus is > 3.5 mg/dL, then restarted at a lower dose after consultation with CCC. On 7/9/2012, the Study Coordinator reduced the dose of ferric citrate by 1 pill per day but continued administration of the study drug.

iii. Subject # (b) (6)-032: Visit 16 (3/21/2012) laboratory testing reported serum phosphorus of 5.7 mg/dL on 3/23/2012. According to the protocol titration schedule, if serum phosphorus is between 5.6 mg/dL and 6.9 mg/dL the ferric citrate dose should be increased by 1 caplet per day. No dose increase was performed.

During the inspection, for KRX-05-305 (4-week study) the FDA field investigator observed the following: the most current informed consent document (ICD) was not used for thirteen subjects. A revised ICD was approved by the IRB on 5/26/10. The revised ICD changed the cost language in the document. The approval did not require re-consent of existing study subjects; however, thirteen subjects consented after the 5/26/2010 were consented using the obsolete 4/16/2010 version.

OSI Reviewer Comments: A Note to File signed by the Study Coordinator was filed in the site's trial master file. Although this is a regulatory violation, this did not affect the safety of subjects enrolled.

Also for KRX-0502-305 (4-week study), the FDA field investigator observed that the dates of participation for study staff on the signature/delegation log were not consistent with the FDA Form 1572 on file at the site.

c. **Assessment of data integrity:** The discrepancies identified during the inspection were discussed verbally with Dr. Schulman and study staff at the conclusion of the inspection. No Form FDA-483 was issued. Upon review of the EIR, OSI has decided to classify this inspection as VAI on the basis of the large number of protocol violations identified for subject records reviewed. Although regulatory violations were found, they are unlikely to significantly impact data integrity. OSI recommends the data is acceptable in support of the respective indication.

2. Mark Smith
815 12th Street
Augusta, GA

a. **What was inspected:** This inspection was conducted according to Compliance Program 7348.811. Dr. Mark Smith has eleven INDs in CDER's COMIS database, and no prior FDA inspection. For Study KRX-0502-304, 55 subjects were screened and 27 subjects enrolled. This inspection was conducted between December 2 and December 6, 2013, and audited these two protocols: KRX-0502-304 (58-week study) and KRX-0502-305 (4-week study).

Under Protocol No. KRX-0502-305, Dr. Smith screened 46 subjects, of which 18 enrolled, and 28 were screen failures. The field investigator reviewed records for eight of the 18 subjects. The first subject was screened on 5/19/2010 and the last subject was screened on 9/18/2010. A total of 18 subjects completed the study.

Under Protocol No. KRX-0502-304, Dr. Smith screened 55 subjects, of which 27 enrolled, and 28 were screen failures. The inspection reviewed ten of the 27 subjects.

There was one death, but it was found not to be related to study drug. The first subject was screened on 1/19/2011 and the last subject was screened on 8/24/2011. A total of 21 subjects completed the study.

The FDA field investigator reviewed the subjects' records and corresponding CRFs for their organization, completeness, and legibility.

This inspection covered the authority and the administration of the clinical study, the study protocol and all amendments, IRB submissions and approvals, subject selection criteria and informed consents, study drug accountability, source data and adverse even reporting. The inspection covered the review of all relevant records consisting of informed consents, protocol amendments, FDA 1572s, financial disclosure forms, IRB approvals and correspondence, eCRFs, and study drug accountability logs.

Paper case report forms were used in both studies, and were completed during the study. Source information was documented, and transcribed onto the paper case report forms by the study coordinator. Data listings provided with the assignment were compared to the source documents and case report forms so that the data could be verified.

b. General Observations/Commentary: No deficiencies were identified with respect to source documentation such as inclusion/exclusion criteria, demographic information, medical history concomitant treatments/medications, adverse event reporting investigational drug administration, or laboratory results. There was no evidence of underreporting of adverse events and all serious adverse events were reported as required per IRB and protocol guidelines. All data was verifiable.

The sponsor, Keryx Pharmaceuticals, Inc. was responsible for its own monitoring. Monitoring staff visited the site approximately every 6-8 weeks. The FDA field investigator observed that many monitoring reports did not arrive at the site until months after the monitoring visit.

No FDA 483, Inspectional Observations was issued, but some discussion items were discussed with the site, including the importance of adhering to the dosing schedule and of accurate data transfer from clinic documents to source documents.

c. Assessment of data integrity: No Form FDA-483 was issued. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. Frederick Whittier
4974 Higbee Ave., NW
Suite 100
Canton, OH 44718

a. What was inspected: This inspection was conducted according to Compliance Program 7348.811. Dr.Whittier has (b) (4) in CDER's COMIS database and no prior inspections. The protocol that was audited was KRX-0502-304 and the inspection took place between January 6 and 9, 2014. A field investigator from the Cincinnati District Office was previously assigned to conduct the inspection of Dr. Whittier, at his office located in Canton, Ohio. Upon contacting the site, she was told that Dr. Whittier had retired and closed down his clinical research site in Ohio, and sent his records for storage at the sponsor location. Therefore, the current inspection was re-issued and a limited clinical investigator inspection of Dr. Whittier's records took place at Keryx Biopharmaceuticals in New York. (b) (4)

At this site, nine subjects were screened and enrolled for the Keryx study. The FDA field investigator conducted a full review of all nine subject records, and compared the source documents against the data listings with regard to randomization, drop-outs, discontinuations, adverse events, protocol violations, primary and secondary efficacy endpoints, concomitant medications, and eligibility criteria.

b. General observations/commentary: The FDA field investigator reported that adverse events were accurately documented and reported, and there was no under-reporting of adverse events. No discrepancies were noted for all other parameters reviewed, including primary and secondary efficacy endpoints. Test article accountability logs were reviewed, and appeared adequate. The CRF's and medical progress notes were handwritten and made by Dr. Whittier and/or a study coordinator. The site did not utilize electronic medical record systems during the study. A Keryx Biopharmaceuticals Monitoring Log was obtained, and the field investigator noted that the monitor made a number of routine visits to the site, and audited all CRFs and patient records during visits. The monitoring appeared adequate.

At the conclusion of the inspection, no FDA 483 was issued.

c. Assessment of data integrity: The study was conducted well at this site, and OSI recommends that the data is acceptable in support of the claimed indication.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three domestic clinical investigator sites were inspected in support of NDA 205874. No regulatory violations were found and no Form FDA 483 was issued during the inspections at

two sites: Dr. Mark Smith and Dr. Frederick Whittier. The inspection of Dr. Gerald Schulman, found a number of protocol violations relating to failure to follow the investigational plan. These observations were discussed at the closeout visit, no Form FDA 483 was issued, and the inspection was initially classified as NAI. However, upon review of the EIR, OSI is giving a final classification of VAI based on the large number of violations identified for subject records reviewed for the KRX-0502-304 (58-Week Study). Although regulatory violations were found, OSI does not consider them significant, and they are unlikely to impact the integrity of the data submitted in support of the claimed indication. OSI recommends the data from these studies may be considered reliable.

{See appended electronic signature page}

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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.

/s/

SHARON K GERSHON
04/02/2014

SUSAN D THOMPSON
04/02/2014

KASSA AYALEW
04/02/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 205874 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: ferric citrate Dosage Form: Tablet Strengths: 1 gram		
Applicant: Keryx Biopharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: 8/7/13 Date of Receipt: 8/7/13 Date clock started after UN:		
PDUFA Goal Date: 6/7/14	Action Goal Date (if different):	
Filing Date: 10/6/13	Date of Filing Meeting: 9/30/13	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 2		
Proposed indication(s)/Proposed change(s): **for the control of serum phosphorus levels** (b) (4) **in patients with chronic kidney disease (CKD) on dialysis.**		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)	

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*):

List referenced IND Number(s): 52868

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	☒	☐		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒	☐	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☒	☐	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***	☐	☒	☐	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒	☐	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***	☐	☒		

Designations and Approvals list at: *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*				
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 5 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☒	☐		

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	Electronic submission
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be*	☒	☐		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	☐	☒	☐	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	☒	☐	☐	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	☒	☐	☐	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL	☒	☐		

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

format? ***If no, request applicant to submit SPL before the filing date.***				
Is the PI submitted in PLR format?[4]	☒			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	☒	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	☐	☐	☐	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If yes, specify consult(s) and date(s) sent:				
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** May 4, 2009	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** March 5, 2013	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** December 30, 2009	☒	☐		

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 30, 2013

NDA #: 205874

PROPRIETARY NAME: (b) (4)

ESTABLISHED/PROPER NAME: ferric citrate

DOSAGE FORM/STRENGTH: 1 gram tablet

APPLICANT: Keryx Biopharmaceuticals, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): indicated for the control of serum phosphorus levels (b) (4) in patients with chronic kidney disease (CKD) on dialysis.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Russell Fortney	Y
	CPMS/TL:	Edward Fromm	
Cross-Discipline Team Leader (CDTL)	Aliza Thompson		
Clinical	Reviewer:	Nancy Xu	Y
	TL:	Aliza Thompson	Y

Clinical Pharmacology	Reviewer:	Ju-Ping Lai	Y
	TL:	Raj Madabushi	
Biostatistics	Reviewer:	John Lawrence	Y
	TL:	Jim Hung	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Rama Dwivedi	
	TL:	Al DeFelice	
Product Quality (CMC)	Reviewer:	Monica Cooper Thomas Wong Vibhskar Shah	
	TL:	Kasturi Srinivasachar	
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Biopharmaceutics	Elsbeth Chikhale TL: Angelica Dorantes		
Other attendees			

FILING MEETING DISCUSSION:

GENERAL	
• 505(b)(2) filing issues:	☐ Not Applicable
○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☒ NO
○ Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	☐ YES ☒ NO
Describe the scientific bridge (e.g., BA/BE studies):	Bridge not needed. Sponsor relies on literature for certain nonclinical studies.
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: none.	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**:	☐ YES Date if known: ☒ NO

If no, for an NME NDA or original BLA , include the reason. For example: ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ To be determined Reason: Not an NME.
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☒ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**: "(b) (4) used in labeling must be corrected to tablet. The sponsor rounded the dosage description to 1 gram (from (b) (4) mg).	☒ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	None.
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Division	

Date of Mid-Cycle Meeting: January 30, 2014 **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST

	eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

RUSSELL FORTNEY
10/29/2013