

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205874Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

1.3. Administrative Information

**PATENT CERTIFICATIONS**

Per 21 CFR 314.50(i)(1)(ii), in the opinion and to the best knowledge of Keryx Biopharmaceuticals, Inc., there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.



\_\_\_\_\_  
Ron Bentsur

Chief Executive Officer

\_\_\_\_\_  
August 2, 2013  
Date

**PATENT INFORMATION SUBMITTED WITH THE FILING  
OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and Composition)  
and/or Method of Use**

NDA NUMBER

205874

NAME OF APPLICANT/NDA HOLDER

Keryx Biopharmaceuticals, Inc

*The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

TRADE NAME (OR PROPOSED TRADE NAME)

(KRX-0502)

ACTIVE INGREDIENT(S)

Ferric citrate coordination complex

STRENGTH(S)

1 gram

DOSAGE FORM

(b) (4)

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number

5,753,706

b. Issue Date of Patent

May 19, 1998

c. Expiration Date of Patent

February 3, 2017

d. Name of Patent Owner

Chen Hsing Hsu

Address (of Patent Owner)

3720 Tremont Lane

City/State

Ann Arbor, Michigan

ZIP Code

48105

FAX Number (if available)

Telephone Number

212-531-5965

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number(s) (as listed in the patent) 1-3, 5 Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) (KRX-0502) is indicated for the control of serum phosphorus levels and the increase in (b) (4) in patients with chronic kidney disease on dialysis, as provided in the proposed labeling, including the Indications and Usage, Dosage and Administration, Clinical Pharmacology, and Clinical Studies sections of the proposed labeling.

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

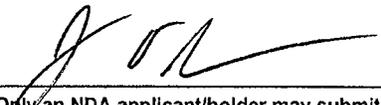
**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



7/29/13

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Keryx Biopharmaceuticals, Inc.

Address

750 Lexington Avenue, 20th Fl

City/State

New York, NY

ZIP Code

10022

Telephone Number

212-531-5965

FAX Number (if available)

212-531-5961

E-Mail Address (if available)

joliviero@keryx.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
Office of Chief Information Officer  
1350 Piccard Drive, Room 400  
Rockville, MD 20850

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 10/31/2013 See OMB Statement on Page 3.	
<b>PATENT INFORMATION SUBMITTED WITH THE FILING          OF AN NDA, AMENDMENT, OR SUPPLEMENT</b>  <i>For Each Patent That Claims a Drug Substance          (Active Ingredient), Drug Product (Formulation and Composition)          and/or Method of Use</i>		NDA NUMBER 205874	
		NAME OF APPLICANT/NDA HOLDER Keryx Biopharmaceuticals, Inc	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) (KRX-0502)			
ACTIVE INGREDIENT(S) Ferric citrate coordination complex		STRENGTH(S) 1 gram	
DOSAGE FORM (b) (4)			
<p>This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.</p> <p><b>For hand-written or typewriter versions (only) of this report:</b> If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.</p> <p><b>FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.</b></p> <p><b>For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.</b></p>			
<b>1. GENERAL</b>			
a. United States Patent Number 7,767,851		b. Issue Date of Patent August 3, 2010	c. Expiration Date of Patent February 18, 2024
d. Name of Patent Owner Panion & BF Biotech, Inc.		Address (of Patent Owner) 16F, NO. 3, Yuanqu Street, Nangang District	
		City/State Taipei	
		ZIP Code Taiwan	FAX Number (if available)
		Telephone Number 886-2-26558218	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)  Keryx Biopharmaceuticals, Inc.		Address (of agent or representative named in 1.e.) 750 Lexington Ave. - 20th Floor	
		City/State New York, NY	
		ZIP Code 10022	FAX Number (if available) 212-531-5961
		Telephone Number 212-531-5965	E-Mail Address (if available) joliviero@keryx.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input type="checkbox"/> No	

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

**5. No Relevant Patents**

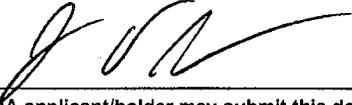
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6. Declaration Certification**

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NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

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Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 10/31/2013 See OMB Statement on Page 3.	
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		NDA NUMBER 205874	
		NAME OF APPLICANT/NDA HOLDER Keryx Biopharmaceuticals, Inc	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) (KRX-0502)			
ACTIVE INGREDIENT(S) Ferric citrate coordination complex		STRENGTH(S) 1 gram	
DOSAGE FORM (b) (4)			
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<b>1. GENERAL</b>			
a. United States Patent Number 8,299,298		b. Issue Date of Patent October 3, 2012	c. Expiration Date of Patent February 18, 2024
d. Name of Patent Owner Panion & BF Biotech, Inc.		Address (of Patent Owner) 16F, NO. 3, Yuanqu Street, Nangang District	
		City/State Taipei	
		ZIP Code Taiwan	FAX Number (if available)
		Telephone Number 886-2-26558218	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)  Keryx Biopharmaceuticals, Inc.		Address (of agent or representative named in 1.e.) 750 Lexington Ave. - 20th Floor	
		City/State New York, NY	
		ZIP Code 10022	FAX Number (if available) 212-531-5961
		Telephone Number 212-531-5965	E-Mail Address (if available) joliviero@keryx.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
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**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

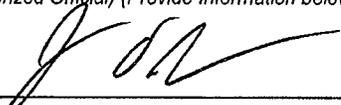
<b>2. Drug Substance (Active Ingredient)</b>	
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2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
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<b>3. Drug Product (Composition/Formulation)</b>	
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
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3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes <input type="checkbox"/> No
<b>4. Method of Use</b>	
<b>Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:</b>	
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4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input type="checkbox"/> Yes <input type="checkbox"/> No
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**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number 8,093,423	b. Issue Date of Patent January 10, 2012	c. Expiration Date of Patent October 19, 2028
d. Name of Patent Owner Panion & BF Biotech, Inc.	Address (of Patent Owner) 16F, NO. 3, Yuanqu Street, Nangang District	
	City/State Taipei	
	ZIP Code Taiwan	FAX Number (if available)
	Telephone Number 886-2-26558218	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)  Keryx Biopharmaceuticals, Inc.	Address (of agent or representative named in 1.e.) 750 Lexington Ave. - 20th Floor	
	City/State New York, NY	
	ZIP Code 10022	FAX Number (if available) 212-531-5961
	Telephone Number 212-531-5965	E-Mail Address (if available) joliviero@keryx.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		
<input type="checkbox"/> Yes <input type="checkbox"/> No		

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number(s) (as listed in the patent) 7-12, 16-22 Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) (KRX-0502) is indicated for the control of serum phosphorus levels and the increase in <sup>(b) (4)</sup> in patients with chronic kidney disease on dialysis, as provided in the proposed labeling, including the Indications and Usage, Dosage and Administration, Clinical Pharmacology, and Clinical Studies sections of the proposed labeling.

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6. Declaration Certification**

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)



Date Signed

7/29/13

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Keryx Biopharmaceuticals, Inc.

Address

750 Lexington Avenue, 20th Fl

City/State

New York, NY

ZIP Code

10022

Telephone Number

212-531-5965

FAX Number (if available)

212-531-5961

E-Mail Address (if available)

joliviero@keryx.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
Office of Chief Information Officer  
1350 Piccard Drive, Room 400  
Rockville, MD 20850

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 10/31/2013 See OMB Statement on Page 3.	
<b>PATENT INFORMATION SUBMITTED WITH THE FILING          OF AN NDA, AMENDMENT, OR SUPPLEMENT</b>  <i>For Each Patent That Claims a Drug Substance          (Active Ingredient), Drug Product (Formulation and Composition)          and/or Method of Use</i>		NDA NUMBER 205874	
		NAME OF APPLICANT/NDA HOLDER Keryx Biopharmaceuticals, Inc	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) (KRX-0502)			
ACTIVE INGREDIENT(S) Ferric citrate coordination complex		STRENGTH(S) 1 gram	
DOSAGE FORM (b) (4)			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.			
<b>For hand-written or typewriter versions (only) of this report:</b> If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
<b>FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.</b>			
<b>For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.</b>			
<b>1. GENERAL</b>			
a. United States Patent Number 8,338,642		b. Issue Date of Patent December 25, 2012	c. Expiration Date of Patent February 18, 2024
d. Name of Patent Owner Panion & BF Biotech, Inc.		Address (of Patent Owner) 16F, NO. 3, Yuanqu Street, Nangang District	
		City/State Taipei	
		ZIP Code Taiwan	FAX Number (if available)
		Telephone Number 886-2-26558218	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)  Keryx Biopharmaceuticals, Inc.		Address (of agent or representative named in 1.e.) 750 Lexington Ave. - 20th Floor	
		City/State New York, NY	
		ZIP Code 10022	FAX Number (if available) 212-531-5961
		Telephone Number 212-531-5965	E-Mail Address (if available) joliviero@keryx.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input type="checkbox"/> No	

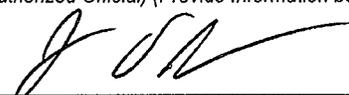
**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

<b>2. Drug Substance (Active Ingredient)</b>	
2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes <input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.	
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes <input type="checkbox"/> No
<b>3. Drug Product (Composition/Formulation)</b>	
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes <input type="checkbox"/> No
<b>4. Method of Use</b>	
<b>Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:</b>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent) 8, 17	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) (KRX-0502) is indicated for the control of serum phosphorus levels and the increase in <sup>(b) (4)</sup> in patients with chronic kidney disease on dialysis, as provided in the proposed labeling, including the Indications and Usage, Dosage and Administration, Clinical Pharmacology, and Clinical Studies sections of the proposed labeling.
<b>5. No Relevant Patents</b>	
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	<input type="checkbox"/> Yes

**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</p> 	<p>Date Signed</p> <p>7/29/13</p>
--	-----------------------------------

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<p>Name Keryx Biopharmaceuticals, Inc.</p>	
<p>Address 750 Lexington Avenue, 20th Fl</p>	<p>City/State New York, NY</p>
<p>ZIP Code 10022</p>	<p>Telephone Number 212-531-5965</p>
<p>FAX Number (if available) 212-531-5961</p>	<p>E-Mail Address (if available) jolviero@keryx.com</p>

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
 Food and Drug Administration  
 Office of Chief Information Officer  
 1350 Piccard Drive, Room 400  
 Rockville, MD 20850

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

1.3. Administrative Information

**3. DEBARMENT CERTIFICATION**

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Keryx Biopharmaceuticals, Inc. 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.



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Ron Bentsur

Chief Executive Officer

*August 2, 2013*

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Date

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION<sup>1</sup>

NDA # 205874 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>				
Proprietary Name: N/A Established/Proper Name: <b>ferric citrate</b> Dosage Form: <b>oral tablet</b>		Applicant: <b>Keryx Biopharmaceuticals, Inc.</b> Agent for Applicant (if applicable): N/A				
RPM:		Division:				
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><b>For ALL 505(b)(2) applications, two months prior to EVERY action:</b></p> <ul style="list-style-type: none"> <li>• Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <p><input checked="" type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i>          Date of check: 7/22/14</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>				
✦ Actions <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 5px;"> <tr> <td style="width: 70%;"> <ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is 7/27/14</li> </ul> </td> <td style="width: 30%;"> <input checked="" type="checkbox"/> AP    <input type="checkbox"/> TA    <input type="checkbox"/> CR           </td> </tr> <tr> <td> <ul style="list-style-type: none"> <li>• Previous actions <i>(specify type and date for each action taken)</i></li> </ul> </td> <td>None</td> </tr> </table>			<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is 7/27/14</li> </ul>	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR	<ul style="list-style-type: none"> <li>• Previous actions <i>(specify type and date for each action taken)</i></li> </ul>	None
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is 7/27/14</li> </ul>	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR					
<ul style="list-style-type: none"> <li>• Previous actions <i>(specify type and date for each action taken)</i></li> </ul>	None					
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received				
❖ Application Characteristics <sup>3</sup>						

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): <b>2</b> ( <i>confirm chemical classification at time of approval</i> )									
<table style="width:100%; border:none;"> <tr> <td style="width:50%; border:none;"><input type="checkbox"/> Fast Track</td> <td style="width:50%; border:none;"><input type="checkbox"/> Rx-to-OTC full switch</td> </tr> <tr> <td style="border:none;"><input type="checkbox"/> Rolling Review</td> <td style="border:none;"><input type="checkbox"/> Rx-to-OTC partial switch</td> </tr> <tr> <td style="border:none;"><input type="checkbox"/> Orphan drug designation</td> <td style="border:none;"><input type="checkbox"/> Direct-to-OTC</td> </tr> <tr> <td style="border:none;"><input type="checkbox"/> Breakthrough Therapy designation</td> <td></td> </tr> </table>		<input type="checkbox"/> Fast Track	<input type="checkbox"/> Rx-to-OTC full switch	<input type="checkbox"/> Rolling Review	<input type="checkbox"/> Rx-to-OTC partial switch	<input type="checkbox"/> Orphan drug designation	<input type="checkbox"/> Direct-to-OTC	<input type="checkbox"/> Breakthrough Therapy designation	
<input type="checkbox"/> Fast Track	<input type="checkbox"/> Rx-to-OTC full switch								
<input type="checkbox"/> Rolling Review	<input type="checkbox"/> Rx-to-OTC partial switch								
<input type="checkbox"/> Orphan drug designation	<input type="checkbox"/> Direct-to-OTC								
<input type="checkbox"/> Breakthrough Therapy designation									
<table style="width:100%; border:none;"> <tr> <td style="width:50%; border:none;">                     NDAs: Subpart H  <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)                 </td> <td style="width:50%; border:none;">                     BLAs: Subpart E  <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)                 </td> </tr> <tr> <td style="border:none;">                     Subpart I  <input type="checkbox"/> Approval based on animal studies                 </td> <td style="border:none;">                     Subpart H  <input type="checkbox"/> Approval based on animal studies                 </td> </tr> </table>		NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520)	BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)	Subpart I <input type="checkbox"/> Approval based on animal studies	Subpart H <input type="checkbox"/> Approval based on animal studies				
NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520)	BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)								
Subpart I <input type="checkbox"/> Approval based on animal studies	Subpart H <input type="checkbox"/> Approval based on animal studies								
<table style="width:100%; border:none;"> <tr> <td style="width:50%; border:none;"> <input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request                 </td> <td style="width:50%; border:none;">                     REMS: <input type="checkbox"/> MedGuide  <input type="checkbox"/> Communication Plan  <input type="checkbox"/> ETASU  <input type="checkbox"/> MedGuide w/o REMS  <input type="checkbox"/> REMS not required                 </td> </tr> </table>		<input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request	REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required						
<input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request	REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required								
Comments:									
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates								
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No								
✦ Public communications ( <i>approvals only</i> )									
<ul style="list-style-type: none"> <li>• Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No								
<ul style="list-style-type: none"> <li>• Indicate what types (if any) of information were issued</li> </ul>	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other – Twitter posting								
❖ Exclusivity									
<ul style="list-style-type: none"> <li>• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?</li> <li>• If so, specify the type</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes								
❖ Patent Information (NDAs only)									
<ul style="list-style-type: none"> <li>• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.								
<b>CONTENTS OF ACTION PACKAGE</b>									
<b>Officer/Employee List</b>									
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included								
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included								

<b>Action Letters</b>	
❖ Copies of all action letters (including approval letter with final labeling)	<b>Included</b>
<b>Labeling</b>	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
<ul style="list-style-type: none"> <li>• Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)</li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	<b>Unacceptable letter, 4/3/13, teleconference minutes 8/26/14 Review2, 10/25/13, 2/7/14</b>
<ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (indicate date(s))</li> <li>• Review(s) (indicate date(s))</li> </ul>	
❖ Labeling reviews (indicate dates of reviews)	RPM: <input checked="" type="checkbox"/> None DMEPA: <input checked="" type="checkbox"/> 5/14/14, 5/22/14, DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: <input checked="" type="checkbox"/> 8/15/14 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input type="checkbox"/> None
<b>Administrative / Regulatory Documents</b>	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting (indicate date of each review)	<b>10/29/13</b>
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<b>9/3/14</b>
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input checked="" type="checkbox"/> Not included – Final document pending mtg with Exclusivity Board
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <b>9/18/13</b> If PeRC review not necessary, explain: _____</li> </ul>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) ( <i>do not include previous action letters, as these are located elsewhere in package</i> )	<b>Included</b>
❖ Minutes of Meetings <ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> <li>• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg <input checked="" type="checkbox"/> 9/19/12, 3/5/13 <input checked="" type="checkbox"/> 5/4/09 <input checked="" type="checkbox"/> N/A <input checked="" type="checkbox"/> N/A N/A
❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> <li>• Date(s) of Meeting(s)</li> </ul>	No AC meeting
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	8/11/14
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	8/8/14
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical</b>	
❖ Clinical Reviews <ul style="list-style-type: none"> <li>• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> <li>• Clinical review(s) (<i>indicate date for each review</i>)</li> <li>• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> No separate review 10/2/13, 4/28/14 <input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input checked="" type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	<b>Clinical review, pages 13 and 84</b>
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A

❖ Risk Management	
<ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<p>N/A</p> <p>N/A</p> <p><input checked="" type="checkbox"/> None</p>
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input checked="" type="checkbox"/> 4/2/14
<b>Clinical Microbiology</b> <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 10/1/13, 4/22/14
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 10/2/13, 6/10/14, 7/23/14
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
<ul style="list-style-type: none"> <li>ADP/T Review(s) (<i>indicate date for each review</i>)</li> <li>Supervisory Review(s) (<i>indicate date for each review</i>)</li> <li>Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)</li> </ul>	<p><input checked="" type="checkbox"/> No separate review</p> <p><input checked="" type="checkbox"/> No separate review</p> <p><input checked="" type="checkbox"/> 8/15/13, 1/16/14</p>
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested

<b>Product Quality</b> <input type="checkbox"/> None	
❖ <b>Product Quality Discipline Reviews</b>	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> 8/30/13, 10/1/13, 3/31/14, 4/2/14, 7/29/14
❖ <b>Microbiology Reviews</b>	<input checked="" type="checkbox"/> 8/9/13
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	
❖ <b>Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer</b> <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ <b>Environmental Assessment (check one) (original and supplemental applications)</b>	
<input checked="" type="checkbox"/> <b>Categorical Exclusion</b> <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	see 3/31/14 review, page 192
<input type="checkbox"/> <b>Review &amp; FONSI</b> <i>(indicate date of review)</i>	N/A
<input type="checkbox"/> <b>Review &amp; Environmental Impact Statement</b> <i>(indicate date of each review)</i>	N/A
❖ <b>Facilities Review/Inspection</b>	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report; date completed must be within <b>2 years</b> of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>5</sup>)</i>	Date completed: <b>12/17/13</b> <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>5</sup> i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

**Day of Approval Activities**

❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input checked="" type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	N/A
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	N/A
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

## MEMORANDUM of TELECONFERENCE

**MEETING DATE:** August 26, 2014  
**TIME:** 11:30 AM - 12:00 PM  
**APPLICATION:** 205874  
**DRUG NAME:** Ferric citrate  
**APPLICANT:** Keryx Biopharmaceuticals, Inc. (Keryx)  
**TYPE OF MEETING:** Guidance

**MEETING CHAIRS:** Lubna Merchant, Pharm.D.  
**MEETING RECORDER:** Karen Bengtson

### FDA ATTENDEES:

Lubna Merchant, Pharm.D. - Associate Director, DMEPA  
Alice Tu, Pharm.D. - Team Leader, DMEPA  
Davis Mathew, Pharm.D. - Safety Evaluator, DMEPA  
Karen Bengtson - Safety Regulatory Project Manager, OSE  
Russell Fortney - Senior Regulatory Project Manager, DCRP

### SPONSOR ATTENDEES:

Ron Bentsur - Chief Executive Officer  
Robert Niecestro, Ph.D. - Head of Regulatory Affairs  
Greg Madison - Chief Operating Officer  
Amit Sharma, M.D. - Vice President, Medical Affairs  
Abe Ceesay - Vice President, Marketing & Operations  
Ed Cullen, Ph.D. - Vice President, Pre-Clinical and Clinical Development  
James Oliviero - Chief Financial Officer

### BACKGROUND:

On November 18, 2013, Keryx submitted the proposed proprietary name Zerenex for review under NDA 205874. The FDA issued a "Proprietary Name Request Conditionally Acceptable" letter for Zerenex on February 11, 2014. Due to a revision in the expression of the tablet strength (i.e., from (b) (4) g to 210 mg), Keryx resubmitted the name for review on May 27, 2014. During a teleconference on July 25, 2014, DMEPA notified Keryx that the name Zerenex was found unacceptable during the second evaluation (see memorandum of teleconference "General Advice Letter" dated 7/29/14 in DARRTS). On July 31, 2014, Keryx submitted a request to withdraw Zerenex along with a new request for proprietary name review for the proposed name " (b) (4) and the alternate name " (b) (4)

### MEETING OBJECTIVES:

To notify Keryx regarding the safety concerns with their proposed primary and alternate proprietary names.

## DMEPA CONCERNS WITH THE PROPOSED NAME(S)

### Primary Proposed Name: (b) (4)

1. The proposed proprietary name, (b) (4) is phonetically similar to the currently marketed product (b) (4). The names are each comprised of three syllables (b) (4) where each syllable sounds similar to each other. The overall phonetic similarity of this name pair is attested by FDA's Phonetic and Orthographic Computer Analysis (POCA) which calculates a 58% combined score and a 63% phonetic match for this name pair. As further testament to the phonetic similarity, two participants in the verbal portion of FDA's prescription simulation study misinterpreted the proposed name as "(b) (4) (one letter off from (b) (4) and three participants misinterpreted the proposed name as "(b) (4) (two letter off from (b) (4). These responses further demonstrated that the first and second syllables of the name pair sound similar (b) (4).

In addition to the phonetic similarity of these names, both products share overlapping product characteristics which increase the potential for error. Both products are available as tablets administered orally.

2. The proposed proprietary name, (b) (4) is orthographically similar to the currently marketed product (b) (4). Both names begin with the same letter "(b) (4) and share orthographically similar infix (b) (4) and suffix (b) (4) when scripted. The overall orthographic similarity of this name pair is attested by FDA's Phonetic and Orthographic Computer Analysis (POCA) which calculates a 51% combined score and a 63% orthographic match for this name pair.

In addition to the orthographic similarity of these names, both products share overlapping product characteristics which increase the potential for error. Both products are available as single strength tablets administered orally, where the strength may be omitted on prescriptions.

### Alternate Proposed Name: (b) (4)

- Inpatient written Rx study: one hit with (b) (4) and two close hits "(b) (4) further suggests potential name confusion with (b) (4).
- POCA search: highest combined score is for (b) (4) 68% combined.

(b) (4)

## REGULATORY OPTIONS

1. Keryx can wait for DMEPA to complete their review of the name and issue a denial letter.
2. Keryx can withdraw the request for proprietary name review (PNR) and submit a prior approval labeling supplement with PNR once an action is taken for NDA 205874.

## DISCUSSION

DMEPA began the teleconference by informing Keryx about the safety concerns with the proposed primary and alternate proprietary names as detailed above and informed them that DMEPA would be issuing a denial letter.

Keryx asked for clarification regarding DMEPA's concern with the orthographic similarity between the proposed name "[REDACTED] (b)(4)" and the marketed product "[REDACTED] (b)(4)" which is an "[REDACTED] (b)(4)". DMEPA explained that prescriptions are sometimes written for over-the-counter medications and there have been examples of it leading to medication errors in the past.

Keryx stated they felt that the dosage strength of 210 mg is very unique and should set them apart from other drugs with similar names and used in different patient populations. DMEPA stated that the simulation study prescription consists of the proposed proprietary name, strength and sig, not just the proposed name. Despite the presence of the 210 mg strength in the simulation study prescription, there was still misinterpretation for "[REDACTED] (b)(4)". Because the likelihood of observing an error in a small study is low, we consider this finding to be an important predictor of errors that could occur in actual use if the proposed name were to be approved and marketed. Keryx stated that they would withdraw the currently proposed name and could be ready to submit additional proposed proprietary names (primary and alternate) by late tomorrow if DMEPA could again expedite their review. DMEPA clarified that there are multiple rate-limiting steps that would make it impossible to complete an adequate review of a proposed name prior to the September 7, 2014, OND PDUFA date.

Keryx asked how they should proceed going forward. DMEPA advised Keryx that they would need to submit updated labeling removing the "[REDACTED] (b)(4)" for the proprietary name and using only the established name (i.e., using only ferric citrate) in advance of the OND PDUFA clock. Further, DMEPA stated that if Keryx's application is to be approved, they can then submit a prior approval labeling supplement with a request for proprietary name review to add a proprietary name.

Keryx stated that not having a proprietary name would delay the launch of their product. DMEPA clarified that a proprietary name is not required to market a drug product and that the decision to not proceed with the launch would be a corporate decision.

Keryx asked how the established name should be presented on the revised labeling. The DCRP RPM stated that he would get that information and provide it to Keryx via email following the teleconference.

## ACTION ITEMS

- The DCRP RPM will provide Keryx with information on how the established name should be presented on labeling in the absence of an approved proprietary name.

- Keryx will submit a request to withdraw the proposed proprietary name, (b) (4) (After meeting comment: Withdrawal submission received 8/26/14)
- If NDA 205874 is approved on or before the September 7, 2014 OND PDUFA goal date, Keryx will follow with the submission of a prior approval labeling supplement and request for proprietary name review.

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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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CHI-MING TU  
09/02/2014

LUBNA A MERCHANT  
09/02/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 205874

**PROPRIETARY NAME REQUEST  
WITHDRAWN**

Keryx Biopharmaceuticals, Inc.  
750 Lexington Avenue  
20<sup>th</sup> Floor  
New York, NY 10022

ATTENTION: James Oliviero, CFA  
Chief Financial Officer

Dear Mr. Oliviero:

Please refer to your New Drug Application (NDA) dated August 6, 2013, received August 7, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ferric Citrate Tablets, 210 mg of ferric iron equivalent to (b) (4) mg of ferric citrate.

We also refer to:

- Your correspondence, dated and received November 18, 2013, requesting review of your proposed proprietary name, Zerenex
- Our correspondence dated February 11, 2014, conditionally accepting your proposed proprietary name, Zerenex
- Your correspondence, dated and received May 27, 2014, resubmitting your proposed proprietary name, Zerenex
- Our teleconference held on July 25, 2014, to discuss DMEPA's reevaluation of the proposed proprietary name, Zerenex
- Your correspondence, dated and received on July 31, 2014, notifying us that you are withdrawing your request for a review of the proposed proprietary name Zerenex
- Your correspondence, dated and received July 31, 2014, requesting review of your proposed proprietary name, (b) (4)

This proprietary name request is considered withdrawn as of July 31, 2014.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Bengtson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3338. For any other information regarding this application, contact Russell Fortney, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1068.

Sincerely,

*{See appended electronic signature page}*

Karen Bengtson  
Safety Regulatory Project Manager  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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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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KAREN E BENGTON  
08/06/2014

## MEMORANDUM of TELECONFERENCE

**MEETING DATE:** July 25, 2014  
**TIME:** 12:30 - 1:00 PM  
**APPLICATION:** NDA 205874  
**APPLICANT:** Keryx Biopharmaceuticals, Inc. (Keryx)  
**DRUG NAME:** Ferric citrate  
**TYPE OF MEETING:** Guidance

**MEETING CHAIRS:** Lubna Merchant, Pharm.D.  
**MEETING RECORDER:** Karen Bengtson

### FDA ATTENDEES:

Lubna Merchant, Pharm.D. - Associate Director, DMEPA  
Alice Tu, Pharm.D. - Team Leader, DMEPA  
Jean Olumba, Pharm.D. - Safety Evaluator, DMEPA  
Karen Bengtson - Safety Regulatory Project Manager, OSE

### SPONSOR ATTENDEES:

#### KERYX

Robert Niecestro - Head of Regulatory Affairs  
Ron Bentsur - Chief Executive Officer  
Greg Madison - Chief Operating Officer  
Brian Adams - General Counsel  
Abe Ceesay - Vice President, Marketing & Operations  
Thomas Cavanagh - Brand Manager  
James Oliviero - Chief Financial Officer

### BACKGROUND:

On November 18, 2013, Keryx submitted the proposed proprietary name Zerenex for review under NDA 205874. The FDA issued a "Proprietary Name Request Conditionally Acceptable" letter for Zerenex on February 11, 2014. Due to a revision in the expression of the tablet strength (i.e., from (b) (4)g to 210 mg), Keryx resubmitted the name for review on May 27, 2014.

### MEETING OBJECTIVES:

To notify Keryx that the proposed proprietary name, Zerenex, has been determined to be unacceptable because it is orthographically similar to the currently marketed product (b) (4)

### DMEPA CONCERNS WITH THE PROPOSED NAME:

We have completed our review of the proposed proprietary name, Zerenex, and have concluded that this name is unacceptable for the following reasons:

- 1) The proposed proprietary name, Zerenex, is orthographically similar to the currently marketed prescription product (b)(4). The orthographic similarity between this name pair stems from both names begin with the same letter (b)(4) contain orthographically similar letters in the (b)(4) position of the name (b)(4) when scripted, and end with the same letter (b)(4). Additionally, both names contain the same number of letters (b)(4). The orthographic similarity between the name pair was also observed from our inpatient prescription simulation study where one participant misinterpreted Zerenex as (b)(4). Because the likelihood of observing an error in a small study is low, we consider this finding to be an important predictor of errors that could occur in actual use if the proposed name were to be approved and marketed. On this basis, we have concerns that the name Zerenex is likely to lead to errors with (b)(4) in actual use. The sample below was used in our inpatient prescription simulation study:

*Zerenex 210mg po TID with meals*

Additionally, as a testament to the orthographic similarity, FDA's Phonetic and Orthographic Computer Analysis (POCA) software calculates a 59% orthographic match for this name pair.

In addition to orthographic similarity, both products have overlapping product characteristics including (b)(4)

## DISCUSSION:

DMEPA informed Keryx that they have completed their review of the proposed proprietary name, Zerenex, and have concluded that this name is unacceptable because Zerenex is orthographically similar to the currently marketed product, (b)(4).

DMEPA acknowledged that this determination differed from their previous evaluation and conclusion communicated in the letter dated February 11, 2014. However, the reason DMEPA reached a different determination with respect to the safety of the proposed name was based upon the new safety information identified in the written simulation studies, which was confirmed by our orthographic analysis of the Zerenex (b)(4) name pair.

In DMEPA's current evaluation of the proposed name, one participant in the written simulation study misinterpreted Zerenex as (b)(4). Because of the small size of these studies (e.g., typically about 250 invited to participate with about 100 responding), it is considered an important predictor of medication errors. In the simulation studies conducted for the previous evaluation, the misinterpretation of Zerenex as (b)(4) did not occur.

Keryx asked why, since (b)(4) has been marketed for some time, did this issue not come up in the last evaluation. DMEPA stated that there are several reasons that could explain why the misinterpretation occurs in one simulation study versus another. The simulation studies were performed using different handwriting and voice samples of the proposed name and the participants responding to the simulation studies differed. Both or either of these changes could explain differences in the qualitative findings of the simulation studies. Additionally, name simulation studies are not designed to provide conclusive evidence that a proposed name does not pose a risk of confusion given the small sample size used in these studies. Therefore, a negative finding (i.e., no name confusion)

from the previous series of prescription simulation studies does not supersede a positive finding (i.e., name confusion) from this subsequent series of simulation studies. Conversely, a positive finding does supersede any previous findings since such a finding is an indication of the vulnerability of a proposed name to confusion.

DMEPA also noted the combine POCA score of close to 60% with this name pair. Keryx asked about the ~60% orthographic and phonetic similarity determined by POCA and how that weighs in the evaluation. Keryx stated that they have had difficulty coming up with a name that has less than 50% orthographic similarity. DMEPA stated that this score indicates two names that are considered "moderately similar." If two names are moderately similar, in the next step, we look at the product characteristics of the drugs (e.g., dosage form, dosage strength, etc.) to see if there is overlap. In this case, both products have overlapping product characteristics including dosage form (tablet), route of administration (oral), frequency of administration (three times daily) and single strengths. The addition of a misinterpretation in the prescription simulation raises concern of medication errors.

Keryx asked what percentage by POCA would be considered "highly similar" and what the likelihood is of that name getting approved. DMEPA stated that >70% would be considered "highly similar" and are at risk for look-alike, sound-alike confusion. In these cases of highly similar names, product characteristics play very little role in mitigating a medication error.

DMEPA referred Keryx to the May 2014 draft guidance titled "Best Practices in Developing Proprietary Names for Drugs" for more information on the methods used by the Agency in the evaluation of a proposed proprietary name.

Keryx asked what the impact would be if there was not an acceptable proprietary name by the September 7, 2014 PDUFA date for their NDA (i.e., would it preclude approval). DMEPA stated that if the Agency were to go towards an approval action and a name was not found acceptable, they could go forward using the established (generic) name for labeling. After approval, Keryx could submit a prior approval supplement for the addition of a proprietary name.

Keryx asked if they could submit multiple names simultaneously for review. DMEPA stated that we only review one name at a time, but encouraged Keryx to submit a primary and alternate proprietary name in their submission. If the first name is found unacceptable, DMEPA will begin preliminary evaluation of the alternate name. In addition, DMEPA recommended that Keryx provide the names via email so that evaluation can begin while waiting on the official submission to be received through the gateway.

Keryx requested that they be able to follow up with DMEPA regarding the status of the review approximately two weeks after it is received. DMEPA stated that they could, but also indicated that DMEPA would be in contact if they identified an issue with the primary proposed name in the preliminary assessment.

## **REGULATORY OPTIONS**

- 1) Withdraw Zerenex and submit an alternate proposed proprietary name.
- 2) Wait for DMEPA to complete the review of the name and issue a denial letter.

## **ACTION ITEMS**

- The OSE SRPM will provide Keyrx with a link to the draft guidance "Best Practices in Developing Proprietary Names for Drugs."

- On July 28, 2014, Keryx will notify DMEPA, through the OSE SRPM, how they plan to proceed (i.e., whether they will withdrawal Zerenex or wait for the denial letter).

**POST-MEETING NOTE:**

On July 28, 2014, Keryx confirmed via email that they have decided to withdraw the proposed name, Zerenex. In addition, they indicated that they will be submitting a new primary and alternate name for consideration during the week.

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/s/  
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KAREN E BENGTSON  
07/29/2014

CHI-MING TU  
07/29/2014

LUBNA A MERCHANT  
07/29/2014

**From:** Bengtson, Karen  
**To:** [joliviero@keryx.com](mailto:joliviero@keryx.com)  
**Cc:** [Fortney, Russell](#)  
**Subject:** NDA 205874 (ferric citrate) - Proposed Proprietary Name  
**Date:** Friday, May 23, 2014 10:49:00 AM

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Dear James,

Given the revision in the expression of the tablet strength for NDA 205874 (i.e., from <sup>(b)</sup><sub>(4)</sub>g to 210 mg), the proprietary name will need to be resubmitted for review as stated in the “Proprietary Name Request Conditionally Acceptable” letter dated February 11, 2014. Please resubmit with the updated information as soon as possible.

Please acknowledge receipt of this email.

Kind regards,  
Karen

Karen Bengtson | Safety Regulatory Project Manager | Office of Surveillance and Epidemiology | CDER | FDA  
10903 New Hampshire Avenue, WO Bldg.22, Room 4483 | Silver Spring, MD 20993  
 301.796.3338 (phone)  [Karen.Bengtson@fda.hhs.gov](mailto:Karen.Bengtson@fda.hhs.gov)



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/s/  
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KAREN E BENGTON  
05/23/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 205874

**REVIEW EXTENSION –  
MAJOR AMENDMENT**

Keryx Biopharmaceuticals, Inc.  
Attention: James Oliviero, CFA  
Chief Financial Officer  
750 Lexington Avenue, 20<sup>th</sup> Floor  
New York, NY 10022

Dear Mr. Oliviero:

Please refer to your New Drug Application (NDA) dated August 7, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zerenex (ferric citrate) Tablets 210 mg.

We have received your submission dated May 15, 2014, which included substantial revisions to the Chemistry, Manufacturing and Controls section of your application. Because this is a major amendment to this application, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is September 7, 2014.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by August 8, 2014.

If you have any questions, please call Russell Fortney, Regulatory Project Manager, at (301) 796-1068.

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.  
Director  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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NORMAN L STOCKBRIDGE  
05/21/2014

**From:** Knight, Yvonne  
**To:** [Oliviero, James \(James.Oliviero@keryx.com\)](mailto:James.Oliviero@keryx.com)  
**Cc:** [Fortney, Russell](#)  
**Subject:** Additional Information Request for NDA 205874 (Prompt Response)  
**Date:** Friday, May 16, 2014 1:55:00 PM  
**Importance:** High

---

Good afternoon Mr. Oliviero,

We have an additional information request concerning Keryx's New Drug Application (NDA) for NDA 205874. We request a prompt response to this IR request.

Your response dated 5/15 to our comment #3 is not acceptable. As mentioned in our T-con, the (b) (4) mg. We recommended that you add another (b) (4) limit (b) (4) you accepted our recommendation. The (b) (4) tablet weight is based on (b) (4) tablets that are formulated to provide 210 mg (as confirmed in our 13-May T-con) of ferric iron assuming (b) (4) assay potency of ferric iron in the ferric citrate drug substance. You should:

1. Recalculate the upper and lower limit of the (b) (4)
2. Revise your back calculations of citrate content and ferric assay content (in your response to Comment #5) to align the acceptance criteria of the drug substance to what would be used in the drug product (b) (4)

Please confirm receipt of this Information Request. Also, please provide me with a courtesy copy via email when you submit your official amendment? If you have any questions or comments feel free to contact me.

Yvonne Knight, MS  
Regulatory Health Project Manager  
Division of New Drug Quality Assessment  
FDA/CDER/OPS/ONDQA  
10903 New Hampshire Avenue  
Bldg. 21, Room 2667  
Silver Spring, MD 20993-0002  
Phone: 301.796.2133  
Email: [yvonne.knight@fda.hhs.gov](mailto:yvonne.knight@fda.hhs.gov)

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/s/  
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YVONNE L KNIGHT  
05/16/2014

**From:** [Knight, Yvonne](#)  
**To:** [Knight, Yvonne](#)  
**Subject:** RE: NDA 205874 - Discipline Review Letter  
**Date:** Thursday, May 08, 2014 7:08:17 AM

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Good morning Mr. Oliviero,

As promised here are the items.

For the T-con scheduled for May 13<sup>th</sup>, we would like to discuss remaining CMC deficiencies and to discuss a path forward. The CMC deficiencies broadly involve the following:

1. Your drug substance batch data demonstrate that the current manufacturing process does not have sufficient control over the citrate assay (w/w%), as batch release results varied from (b) (4) (38 batches). This inconsistency and wide range for citrate content has (b) (4) impacts on the drug product (refer to deficiency #2 below) with regard to the tablet size, weight, and performance.
2. Your drug product control strategy is inadequate to assure consistent drug product quality. Because the drug substance acceptance criteria for ferric iron assay ranges from (b) (4) % w/w and the citrate assay can range from (b) (4) %, the total tablet weight could range from (b) (4) mg, when formulating the tablet for 210 mg of ferric iron. This range in tablet weight could have an impact on tablet sizes that is apparent to the patient and could have an impact on product performance (dissolution) due to different tablet hardness.
3. In your NDA Amendment dated 04-Mar-2014, you provided data from the drug substance forced degradation study. The amendment contained insufficient data to determine if the method is stability indicating.
4. As communicated in the 09-Apr-14 discipline review letter, we do not agree with your current expression of tablet strength throughout the labeling. Revise the potency in the bottle and box labels from (b) (4) mg to 210 mg.

Tentative Attendees:

Olen Stevens, PhD      Acting Branch Manager  
Kasturi Srinivasachar, PhD      CMC Lead  
Monica Cooper, PhD,      CMC Reviewer  
Thomas Wong, PhD,      CMC Reviewer  
Yvonne Knight, MS      Project Manager

Best Regards,

*Yvonne Knight*

---

**From:** Knight, Yvonne

**Sent:** Wednesday, May 07, 2014 3:25 PM  
**To:** 'Oliviero, James'  
**Subject:** RE: NDA 205874 - Discipline Review Letter

Good afternoon Mr. Oliviero,

I will be able to provide you with further information no later than tomorrow morning if not later this evening. I will also include my list of attendees at that time.

Best Regards,

*Yvonne Knight*

---

**From:** Oliviero, James [<mailto:James.Oliviero@keryx.com>]  
**Sent:** Wednesday, May 07, 2014 12:54 PM  
**To:** Knight, Yvonne  
**Subject:** Re: NDA 205874 - Discipline Review Letter

Dear Ms. Knight,

With regard to the teleconference scheduled for May 13, 2014, at 10am ET, the attendees from Keryx will be:

Pushpa Singh, Vice President, Quality Operations & CMC Regulatory  
Henry Le, Vice President, CMC Operations  
Charles Olson, Senior Director, CMC Analytical Development  
Doris Chen, Director, Quality Operations  
James Oliviero, Chief Financial Officer

Could you please confirm the participants from the FDA? In addition, as we discussed on the phone last week, we would greatly appreciate receiving further information on the topics/issues to be discussed on the teleconference to ensure that we are adequately prepared for the discussion.

Best regards,  
James

James F. Oliviero, CFA  
*Chief Financial Officer*  
Keryx Biopharmaceuticals, Inc.  
750 Lexington Avenue, 20th Floor  
New York, NY 10022  
(212) 531-5970 (Tel)  
(212) 531-5961 (Fax)  
[joliviero@keryx.com](mailto:joliviero@keryx.com)

**From:** Oliviero, James  
**Sent:** Friday, May 02, 2014 9:42 AM  
**To:** 'Knight, Yvonne'  
**Subject:** RE: NDA 205874 - Discipline Review Letter

Dear Ms. Knight,

Our team is available to meet on May 13, 2014, at 10am ET. We can use the below call-in numbers:

US Toll-Free: 1-888-864-0816  
US Toll: 1-719-234-7888  
Participant Passcode: 399814

Would it be possible for me to give you a call today with a few questions on the background for the call so that we are properly prepared? Please let me know what time is most convenient for you.

Best regards,  
James

**From:** Knight, Yvonne [<mailto:Yvonne.Knight@fda.hhs.gov>]  
**Sent:** Friday, May 02, 2014 8:31 AM  
**To:** Oliviero, James  
**Cc:** Knight, Yvonne  
**Subject:** RE: NDA 205874 - Discipline Review Letter  
**Importance:** High

Good Morning Mr. Oliviero,

The Agency would like to have a teleconference with you regarding CMC issues. Is your team available to meet on May 13, 2014 at 10 AM (EST)? Please let me know at your earliest convenience.

Best Regards,

*Yvonne Knight*

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/s/  
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YVONNE L KNIGHT  
05/13/2014

**From:** Knight, Yvonne  
**To:** [Oliviero, James \(James.Oliviero@keryx.com\)](mailto:James.Oliviero@keryx.com)  
**Cc:** [Fortney, Russell](#)  
**Subject:** Information Request for NDA 205874 (Prompt Response)  
**Date:** Tuesday, May 13, 2014 2:06:00 PM  
**Importance:** High

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Good afternoon Mr. Oliviero,

Following our teleconference, 13-May-14, submit the following items as a formal amendment to your NDA 205874 for Ferric citrate:

1. Include a statement confirming that all batches were manufactured targeting 210 mg ferric iron.
2. Clearly denote the drug product batches and stability batches that were manufactured with the current drug substance manufacturing process (b) (4)
3. Put a control limit on the (b) (4) tablet (b) (4) weight to (b) (4) % of the (b) (4) tablet (b) (4) weight.
4. Update (b) (4) controls for (b) (4) tablet weight from (b) (4)
5. Back calculate citrate content and ferric assay content to align the acceptance criteria of the drug substance to what would be used in the drug product process.
6. Update the formula, process description, expression of assay for all applicable sections of your NDA.
7. As best as you can, account for the (b) (4) differences observed in the forced degradation studies.
8. Indicate the tests that will be performed during drug substance retest (specifically noting that (b) (4) will be tested).

Please confirm receipt of this Information Request. Also, please provide me with a courtesy copy via email when you submit your official amendment? If you have any questions or comments feel free to contact me.

Yvonne Knight, MS  
Regulatory Health Project Manager  
Division of New Drug Quality Assessment  
FDA/CDER/OPS/ONDQA  
10903 New Hampshire Avenue  
Bldg. 21, Room 2667  
Silver Spring, MD 20993-0002  
Phone: 301.796.2133  
Email: [yvonne.knight@fda.hhs.gov](mailto:yvonne.knight@fda.hhs.gov)

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YVONNE L KNIGHT  
05/13/2014



NDA 205874

**DISCIPLINE REVIEW LETTER**

Keryx Biopharmaceuticals, Inc.  
Attention: James Oliviero, Chief Financial Officer  
750 Lexington Avenue  
20<sup>th</sup> Floor  
New York, NY 10022

Dear Mr. Oliviero:

Please refer to your New Drug Application (NDA) dated August 6, 2013, received August 7, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ferric citrate tablets (KRX-0502).

We also refer to your amendments dated August 21, 2013, November 4, 2013, February 14, 2014, March 4, 2014, and March 21, 2014.

Our review of the Chemistry, Manufacturing, and Controls section of your submission is complete, and we have identified the following deficiencies:

1. Please clarify the conditions under which the (b) (4) intermediate will be stored for the (b) (4) hold time.
2. We do not agree with your proposal to (b) (4). Add this test, method, and acceptance criteria (b) (4) and continue monitoring this impurity in every batch at release.
3. Your drug substance specification limits for ferric iron assay ((b) (4) % w/w) are (b) (4) and preclude formulation of the drug product (tablet) with a specific amount of ferric iron (e.g., 210 mg). Define a specific target for the amount of ferric iron in the drug substance (e.g., (b) (4) % w/w) and propose tight acceptance ranges to control the amount of ferric iron batch-to-batch.
4. In your NDA Amendment dated 04-Mar-2014, you provided data from the drug substance forced degradation study. (b) (4) was not achieved for several of the forced degradation/stress studies (b) (4). In addition, you did not analyze the (b) (4) formed under several of the conditions. Therefore, you have not shown your citrate-related impurity method to be stability-indicating. Repeat the forced degradation study analyzing any (b) (4),

etc. and determine if (b) (4) can be achieved with the current impurity method. If not, (b) (4) methods should be developed to accurately quantitate all potential impurities of the drug substance.

5. Because out-of-specification citrate content results were observed for several primary and validation stability batches (Lots 35102, 35106, and 38404) at various stability time points, including the initial time point (t=0), no retest date can be given to the ferric citrate drug substance. Better control of the citrate content should be demonstrated at release and during stability studies.
6. We do not agree with your current expression of tablet strength throughout the labeling. Revise the tablet strength to “Each BRAND tablet contains 210 mg of ferric iron equivalent to (b) (4) mg of ferric citrate.”

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, contact Yvonne Knight, Regulatory Project Manager, at (301) 796-2133.

Sincerely,

*{See appended electronic signature page}*

Olen Stephens, Ph.D.  
Acting Branch Chief  
Branch I, Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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OLEN M STEPHENS  
04/09/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 205874

**MEETING MINUTES**

Keryx Biopharmaceuticals, Inc.  
Attention: James Oliviero, CFA  
Chief Financial Officer  
750 Lexington Avenue, 20<sup>th</sup> Floor  
New York, NY 10022

Dear Mr. Oliviero:

Please refer to your New Drug Application (NDA) dated August 7, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for ferric citrate tablets (KRX-0502).

We also refer to the teleconference between representatives of your firm and the FDA on February 28, 2014.

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

If you have any questions, please call Russell Fortney, Regulatory Project Manager, at (301) 796-1068.

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.  
Director  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURE:  
Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** February 28, 2014  
**Meeting Location:** Teleconference

**Application Number:** NDA 205874  
**Product Name:** Ferric citrate tablets (KRX-0502).  
**Sponsor/Applicant Name:** Keryx Biopharmaceuticals, Inc.

**Meeting Chair:** Norman Stockbridge  
**Meeting Recorder:** Russell Fortney

### FDA PARTICIPANTS

#### *Division of Cardiovascular and Renal Products*

Norman Stockbridge, MD, PhD Director  
Aliza Thompson, MD Medical Team Leader  
Nancy Xu, MD Medical Reviewer  
Russell Fortney Regulatory Project Manager

#### *Office of Clinical Pharmacology*

Rajanikanth Madabushi, PhD Team Leader  
Ju-Ping Lai, PhD Reviewer

### KERYX PARTICIPANTS

Robert Niecestro, PhD Regulatory Consultant  
Ed Cullen, PhD Vice President, Pre-Clinical and Clinical Development  
Ron Bentsur Chief Executive Officer  
James Oliviero Chief Financial Officer

### BACKGROUND

Ferric citrate is a phosphate binder proposed for the control of serum phosphorus levels (b) (4) in patients with chronic kidney disease on dialysis. Keryx submitted NDA 205874 on August 7, 2013. On November 26, 2013, the Division informed Keryx that it was not sufficient to perform visual evaluation for precipitation in their in vitro drug-drug interaction (DDI) studies. The Division further advised Keryx to repeat their in vitro studies with drugs that did not show precipitation and measure free drug concentrations in the presence and absence of ferric citrate at the proposed maximum dose under conditions mimicking physiological conditions. Keryx submitted a revised proposal on December 10, 2013. In its January 14, 2014, response, the Division indicated that the revised proposal was not acceptable. Keryx requested this teleconference to discuss a path forward regarding the DDI studies. Preliminary responses to Keryx's questions were communicated to Keryx prior to the teleconference and are attached to these minutes for reference.

### MEETING

After introductions, Dr. Stockbridge stated that the Division had reviewed the submitted slides and was in agreement with most aspects of their proposal. Dr. Madabushi provided the following comments and recommendations:

- (b) (4) is contraindicated in end-stage renal disease. It should be removed from the list on slide #24 and replaced with amlodipine.

- It is sufficient to conduct the tests at pH 4.5 and 6.8; testing at pH 2 is not physiologically relevant because ferric citrate will be given with food and gastric pH increases to 4.5 in the presence of food.
- Consider conducting the tests in the presence of phosphate (375 – 400 mg).

Keryx asked if all of the drugs listed on slide #24 needed to be tested. The Division stated that all of the listed drugs should be tested, with the following exceptions:

- Vitamin D analogues – can be tested sequentially until one is identified that does not interact; additional candidates beyond those listed do not need to be tested, even if all of the listed analogues show an interaction
- Statins – can be tested sequentially until one is identified that does not interact; again, additional candidates beyond those listed do not need to be tested

Keryx noted that they have experienced solubility issues with digoxin. They asked what should be done if they are unable to overcome this issue. Dr. Madabushi stated that Keryx should be able to overcome this problem by increasing the media volume. He also noted that if they cannot conduct the test adequately it could be handled in labeling.

The Division stated that when the DDI results are submitted Keryx should also submit an updated label containing appropriate revisions.

Keryx stated that their goal is to submit the results by May 7, 2014, and asked whether the submission would affect the PDUFA goal date. Dr. Thompson stated that the Division will not know the answer to that question until the data are submitted and reviewed.

**ATTACHMENTS: Preliminary Responses, Sponsor's slides**



NDA 205874

**MEETING – PRELIMINARY COMMENTS**

Keryx Biopharmaceuticals, Inc.  
Attention: James Oliviero, CFA  
Chief Financial Officer  
750 Lexington Avenue, 20<sup>th</sup> Floor  
New York, NY 10022

Dear Mr. Oliviero:

Please refer to your New Drug Application (NDA) dated August 7, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for ferric citrate tablets (KRX-0502).

We also refer to our information requests communicated to you via email on November 26, 2013 and January 14, 2014 regarding the drug-drug interaction studies for KRX-0502.

Finally, we refer to the teleconference scheduled for February 28, 2014, and the questions you submitted in advance of the teleconference.

We have the following comments and responses:

We believe it is critical to characterize the drug-drug interaction potential of KRX-0502 prior to marketing. Polypharmacy is common in the target patient population and it is important to determine whether there are clinically important interactions between KRX-0502 and medications that are frequently used in this population. There are other approved phosphate binders and your therapy does not address an unmet medical need; hence we think this issue needs to be resolved prior to marketing

1. Does FDA agree with Keryx's proposal to [redacted] (b) (4) as a way to address the potential for drug-drug interactions with KRX-0502?

**Agency response:** No, we do not believe that the [redacted] (b) (4) will produce the desired information. [redacted] (b) (4)

2. Does FDA agree with Keryx's proposal to [redacted] (b) (4) as a way to address the potential for drug-drug interactions with KRX-0502?

**Agency response:** Please see our response to Question 1.

3. Does FDA agree with Keryx's proposal to [redacted] (b) (4) as a way to address the potential for drug-drug interactions with KRX-0502?

**Agency response:** Please see our response to Question 1.

4. Does FDA think that the information provided by the proposed analyses of the Study 304 database, together with the *in vitro* data already submitted, are sufficient to support approval of the NDA?

**Agency response:** No. We still believe you need to identify at least one drug per class which does not show an interaction. Classes of medications that are commonly used in the target population are provided below. You may already have results for some of these classes; further characterization is needed for classes lacking conclusive results.

- Antidiabetics
- Antihypertensives
- Antihyperlipidemics
- Antibiotics
- Warfarin and other anticoagulants/anti-platelets
- Digoxin
- Vitamin D analogues

5. Does FDA anticipate requesting additional drug-drug interaction studies as Phase 4 (post-marketing) commitments?

**Agency response:** We expect that you will generate the necessary *in vitro* interaction information prior to approval. Depending on the scope and timing of your response, we may decide this is a major amendment, which would extend the goal date, or review your submission in a second cycle.

Please provide a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, please call Russell Fortney, Regulatory Project Manager, at (301) 796-1068.

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.  
Director  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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NORMAN L STOCKBRIDGE  
03/31/2014

**From:** [Oliviero, James](#)  
**To:** [Knight, Yvonne](#)  
**Cc:** [Singh, Pushpa](#)  
**Subject:** RE: Information Request for NDA 205874 (Prompt Response)  
**Date:** Thursday, March 20, 2014 3:06:21 PM

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Dear Ms. Knight,

Your email below is received. We will address the below request by Monday, March 24<sup>th</sup>.

Best regards,  
James

---

**From:** Knight, Yvonne [mailto:Yvonne.Knight@fda.hhs.gov]  
**Sent:** Thursday, March 20, 2014 3:03 PM  
**To:** Oliviero, James  
**Cc:** Knight, Yvonne  
**Subject:** Information Request for NDA 205874 (Prompt Response)  
**Importance:** High

Good Afternoon Mr. Oliviero,

We have an information request concerning Keryx's New Drug Application for (NDA) NDA 205874. We request a prompt response to this IR by **COB Monday March 24, 2014**.

We acknowledge the information that you submitted on March 18, 2014 in response to our telephone conference on March 13, 2014. Taking into consideration all the provided information, we have determined that a dissolution acceptance criterion of  $Q = \frac{(b)}{(4)}\%$  at 45 minutes is acceptable for your drug product.

1. Please submit a revised drug product specification table and revised stability protocol, reflecting this revised dissolution acceptance criterion.

Please confirm receipt of this Information Request. Also, please provide me with a courtesy copy via email when you submit your official amendment? If you have any questions or comments feel free to contact me.

Best Regards,

Yvonne Knight, MS  
Regulatory Health Project Manager  
Division of New Drug Quality Assessment  
FDA/CDER/OPS/ONDQA

10903 New Hampshire Avenue  
Bldg. 21, Room 2667  
Silver Spring, MD 20993-0002  
Phone: 301.796.2133  
Email: [yvonne.knight@fda.hhs.gov](mailto:yvonne.knight@fda.hhs.gov)

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/s/  
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YVONNE L KNIGHT  
03/20/2014

**From:** [Oliviero, James <joliviero@keryx.com>](mailto:joliviero@keryx.com)  
**To:** [Bengtson, Karen](mailto:Karen.Bengtson@fda.hhs.gov)  
**Cc:** [Fortney, Russell](mailto:Fortney.Russell@fda.hhs.gov)  
**Subject:** RE: NDA 205874 (ferric citrate coordination complex - Regarding your Request for Proprietary Name Review  
**Date:** Monday, February 03, 2014 1:01:24 PM

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Dear Karen,

Thank you for your email. We have discussed internally, and would like DMEPA to continue with the proprietary name evaluation of Zerenex.

Best regards,  
James

James F. Oliviero, CFA  
*Chief Financial Officer*  
Keryx Biopharmaceuticals, Inc.  
750 Lexington Avenue, 20th Floor  
New York, NY 10022  
(212) 531-5970 (Tel)  
(212) 531-5961 (Fax)  
[joliviero@keryx.com](mailto:joliviero@keryx.com)

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**From:** Bengtson, Karen [mailto:Karen.Bengtson@fda.hhs.gov]  
**Sent:** Monday, February 03, 2014 11:21 AM  
**To:** Oliviero, James <joliviero@keryx.com>  
**Cc:** Fortney, Russell  
**Subject:** NDA 205874 (ferric citrate coordination complex - Regarding your Request for Proprietary Name Review  
**Importance:** High

Dear James,

During our evaluation of your proposed proprietary name, Zerenex, we identified a foreign name

(b) (4)

While these international names will not affect the acceptability of your proposed name in the US, using a proprietary name in the US that is identical to or almost identical in spelling or pronunciation to a foreign name may inhibit your ability to obtain a global proprietary name, if that is your goal.

Would you like DMEPA to continue with our proprietary name evaluation of Zerenex? We request a response by COB Tuesday, February 3, 2014.

Please confirm receipt of this email.

Kind regards,

Karen

Karen Bengtson | Safety Regulatory Project Manager | Office of Surveillance and Epidemiology | CDER | FDA  
10903 New Hampshire Avenue, WO Bldg.22, Room 4483 | Silver Spring, MD 20993

 301.796.3338 (phone)  [Karen.Bengtson@fda.hhs.gov](mailto:Karen.Bengtson@fda.hhs.gov)



consider the environment before printing this e-mail

The information contained in this message and any attachment(s) may be privileged and/or confidential and is intended for the addressee(s) only. It may contain legally privileged and protected information. If you are not the intended recipient, you are hereby notified that any review, disclosure, reproduction, distribution, or other use of this communication is strictly prohibited. If you received this email in error, please notify the sender by reply, and immediately delete the message without saving, copying, or disclosing it. Unauthorized disclosure may result in legal liability for those persons responsible. Thank you.

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/s/  
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KAREN E BENGTSON  
02/11/2014



NDA 205874

**INFORMATION REQUEST**

Keryx Biopharmaceuticals, Inc.  
Attention: James Oliviero, Chief Financial Officer  
750 Lexington Avenue  
20th Floor  
New York, NY 10022

Dear Mr. Oliviero:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for KRX-0502 (ferric citrate) Tablet, 210 mg.

We also refer to your August 7, 2013, submission.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA by Monday COB March 3, 2014.

Drug Substance

1. In Section S.2.3, in your specification for the starting material (b)(4) (b)(4) uses a (b)(4) for identification. The USP monograph for (b)(4) indicates (b)(4) should be used for identification. Update the (b)(4) specification from (b)(4) to comply with the current USP monograph, which uses IR for identification.
2. In Sections S.2.3, S.3.2, and S.4.1, you provide limits for (b)(4) in the starting material (b)(4) and the drug substance ferric citrate that you state are derived from the draft USP (b)(4) chapter. However, there are differences between the oral permitted daily exposure limits (PDEs) for (b)(4) in the draft USP (b)(4) chapter and in your proposal (e.g., Tables 4 and 5 of Section S.2.3). Specifically, the draft USP (b)(4) oral PDEs are (b)(4). (b)(4) e-calculate the (b)(4) limits in the starting material (b)(4) and the drug substance ferric citrate based on the lower PDEs and revise your acceptance criteria accordingly.

3. In Section S.2.4, you state that (b) (4) is not an (b) (4) intermediate. However, you indicate that the hold time for the (b) (4) is (b) (4) days. Provide data to support this (b) (4) hold time.
4. In Section S.2.6, you propose to use (b) (4). Provide the comparative data used to assess the (b) (4) drug substance manufactured with the (b) (4). Also, provide representative certificates of analysis for the two (b) (4) specifically indicating their purity.
5. In Section S.3.2 you propose to (b) (4). This proposal is not acceptable. Add this test to your drug substance regulatory specification (in Section S.4.1). Collect the data on the first (b) (4) commercial batches. Depending on these results, you may consider resubmitting your proposal to discontinue this test or propose to continue testing with a better method.
6. Regarding the drug substance specification:
  - a. Your proposed limit for (b) (4) content (NMT (b) (4) % w/w) is not justified. Batch results were (b) (4) % and the mean ( (b) (4) % w/w) plus (b) (4) standard deviations was (b) (4) %. Therefore, tighten the limit to NMT (b) (4) % w/w.
  - b. You did not provide adequate justification for your proposed particle size distribution acceptance criterion of D90: NMT (b) (4) μm. The levels observed in all 38 batches were ≤ (b) (4) μm. Since the particle size distribution is important to (b) (4) drug product, the acceptance criteria should reflect the levels necessary for drug product manufacturing. Therefore, tighten your limit for D90 accordingly and provide tablet dissolution profiles to support your revised limit.
  - c. You did not provide adequate justification for your proposed (b) (4) specific surface area acceptance criterion of NLT (b) (4). The lowest level observed in your batches to date is (b) (4) and the mean minus (b) (4) STDs is (b) (4). Tighten your specification limit to reflect levels necessary for drug product manufacturing.
  - d. You propose a (b) (4) % w/w limit for (b) (4) in the drug substance. However, per the validation report, the acceptable range for the (b) (4) method is (b) (4) %. Also, after the (b) (4). Therefore, tighten your proposed limit to correspond to the method capability and recent process improvements.
  - e. Include a specification limit for total impurities that includes both known and unknown impurities.

7. Explain why you did not test particle size distribution or (b) (4) surface area in your stability studies, as these attributes have been found to affect drug product manufacturability and dissolution rate.
8. In Section S.7.1 you provide a narrative summary of the forced degradation studies performed on Batch 37768. Provide the data from this study, showing the (b) (4) achieved between assay and impurities/degradants.
9. In Section S.7.2, you provide a post-approval stability protocol for ferric citrate drug substance. Please revise the protocol to include the stability time points of (b) (4) months per ICH Q1A (R2).
10. In Section S.7.3, you provide stability results for primary and validation stability batches using multiple (b) (4) methods for citrate content and citrate-related impurities. Please address the following:
  - a. Significant levels of many impurities were observed using the previous (b) (4) methods (b) (4). However, using the new (b) (4) method (b) (4) you do not observe numerous impurities.
    - i. Explain the absence of other impurities using the new (b) (4) method.
    - ii. Compare the stability results by the old and new (b) (4) methods by conducting a bridging study using the previous (b) (4) and current (b) (4) methods at your next stability time point.
    - iii. Correlate historical stability data using the results of this bridging study.
  - b. Using the new (b) (4) method (b) (4) citrate content was out-of-specification (OOS) for Batch 38404 at the (b) (4) month time point at both long-term and accelerated conditions. Clarify whether an investigation was performed. In addition, citrate content was OOS at (b) (4) months for Batch 35106 and at (b) (4) months for Batch 35102 using the previous (b) (4) method. Retains of these batches tested using the new (b) (4) method did not show significantly different values and continued to be OOS for Batch 35106. Justify why the stability data with these OOS results support a retest date for the drug substance.

## Drug Product

### Composition of the drug product:

11. Remove the ingredient ranges from the composition of the ferric citrate tablet. It is not acceptable to have a (b) (4)

### Manufacturing process development:

12. Provide rationale for establishing the (b) (4) limit of NMT (b) (4) % w/w for the (b) (4) (b) (4). Include data to show the dissolution rate of the (b) (4) tablet with a function of % (b) (4).

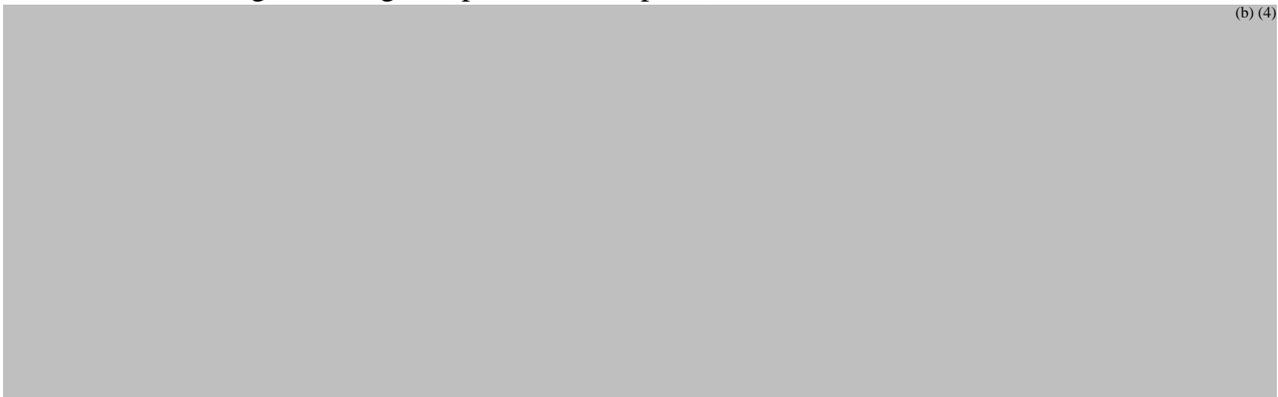
13. Provide rationale for choosing (b) minutes as the (b) (4) time of the (b) (4). Include data to show the dissolution rate and hardness of the (b) (4) tablets as a function of (b) (4) time.

Batch formula:

14. Provide specific commercial batch sizes to be manufactured. It is not acceptable to provide commercial batch size with a range.

Description of manufacturing process and process controls:

15. Include the following equipment type, size and processing parameters in the product manufacturing flow diagram, process description, and master batch record:



16. Confirm that the master batch record for use in the commercial manufacturing of the drug product is identical to the executed batch record provided for lot # 555043 with the exception of the details that will be added in response to the information requests (#14 and #15) above.
17. Provide processing parameters that were entered into the recipe used for ferric citrate tablets in Step # 14.2.2 of the executed batch record for lot # 555043.

Drug product specification:



19. Rename the testing for "individual other impurities" to "individual unspecified impurities".
20. Change the acceptance criterion for the Individual Other Impurities from (b) (4) to % w/w to be consistent with the units for the specified impurities and to comply with ICH Q3B guidance.
21. The submitted dissolution data do not support your proposed dissolution acceptance criterion of  $Q = \frac{(b)}{(4)}\%$  at (b) (4) minutes and is not acceptable. Based on the data, a dissolution acceptance criterion of  $Q = \frac{(b)}{(4)}\%$  at (b) (4) minutes should be implemented for your product. Revise your drug product specification and stability protocol accordingly and submit a copy of the updated specification table.

Validation of analytical procedures:

22. On page 1351 of the file in Section 3.2.P.5.3, your application states that validation report (b) (6) is a supplemental validation emphasizing impurities and supplements previous validation of method (b) (4) using the same chromatography, which emphasized the precision, linearity, accuracy and stability-indicating characteristics of the citrate content determination. The protocol for the previous validation of method (b) (6) is not provided in the submission. Provide the original validation reports for method (b) (6)

Batch analysis:

23. In your batch analysis data for the drug product, significant levels of many other individual impurities were observed in retains of earlier lots when tested by the previous (b) (4) method (b) (4) but were not observed when tested by the current (b) (4) method (b) (4). Explain the absence of the other impurities using the new (b) (4) method.

Container closure system:

24. Provide (b) (4) data for the (b) (4) HDPE bottle.
25. Provide food contact compliance statements/information for the HDPE bottles and child-resistant caps to be used for packaging of the commercial tablets.

Stability:

26. Clarify which type of HDPE bottles, (b) (4) were used in the primary and in the supportive stability studies.
27. The primary registration and supportive stability results indicate that many of the other individual impurities failed the drug product release specification of NMT (b) (4) % area. Explain the OOS.
28. To compare the drug product stability results of all three registration batches by the old and new (b) (4) methods, conduct a bridging study using the previous (b) (4) and current (b) (4) methods at your next stability time point. Provide the comparative data within three months from the receipt of this comment.
29. Your proposed shelf-life of (b) (4) months for the drug product is not acceptable. The stability data obtained from (b) (4) cannot be used for predicting shelf-life by (b) (4) due to dissolution failure. Additional real time stability data can be provided, which will be reviewed as resources allow.

Labeling and package insert:

30. Edit the expression of the tablet strength to “Each BRAND tablet contains 210 mg of ferric iron equivalent to (b) (4) mg of ferric citrate.”
31. In the labeling text, bottle and box labels, you need to mention the presence of FD&C Yellow No. 6 in the coating material that contains this colorant according to CFR 201.20 (c).
32. Refer to the edited version of your package insert that was sent with this information request. Incorporate the edits made in this attached file into your package insert. Also, make the corresponding changes to the bottle container and carton labels, accordingly.

Submit revised content of labeling 21 CFR 201.100(d)(3) in structured product labeling (SPL) format as described at: <http://www.fda.gov/oc/datacouncil/spl.html>.

If you have any questions, call Yvonne Knight, Regulatory Project Manager, at (301) 796-2133.

Sincerely,

*{See appended electronic signature page}*

Olen Stephens, Ph.D.  
Acting Branch Chief  
Branch I, Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Enclosure:  
Labeling Text Revisions

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

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/s/  
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OLEN M STEPHENS  
02/04/2014



NDA 205874

**FILING COMMUNICATION –  
NO FILING REVIEW ISSUES IDENTIFIED**

Keryx Biopharmaceuticals, Inc.  
Attention: James Oliviero, CFA  
Chief Financial Officer  
750 Lexington Avenue, 20<sup>th</sup> Floor  
New York, NY 10022

Dear Mr. Oliviero:

Please refer to your New Drug Application (NDA) dated August 7, 2013, received August 7, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for ferric citrate coordination complex.

We also refer to your amendments dated August 20, 21, 30, October 3, 4, and 9, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is June 7, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by May 9, 2014.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. Provide a copy of the letter designating the USAN name of the drug substance. Neither ferric citrate nor ferric citrate coordination complex was found in the current USP Dictionary.
2. Please submit labeling revised as follows:
  - a. The term (b) (4) is not recognized by USP as an official solid oral dosage form designation. Revise the dosage form to 'tablet' throughout the labeling.

- b. The strength of the tablet should be expressed in milligrams of elemental iron equivalent to (b) (4) mg of ferric citrate. Revise the labeling accordingly.

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

### **PROMOTIONAL MATERIAL**

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

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

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

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

### **REQUIRED PEDIATRIC ASSESSMENTS**

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

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

If you have any questions, please call Russell Fortney, Regulatory Project Manager, at (301) 796-1068.

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.  
Director  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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NORMAN L STOCKBRIDGE  
10/18/2013



NDA 205874

**INFORMATION REQUEST**

Keryx Biopharmaceuticals, Inc.  
Attention: James Oliviero, Chief Financial Officer  
750 Lexington Avenue  
20<sup>th</sup> Floor  
New York, NY 10022

Dear Mr. Oliviero:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for KRX-0502 (ferric citrate coordination complex) (b) (4) 1g.

We also refer to your August 7, 2013, submission.

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

1. Submit the dissolution method development report which should include the following:
  - a. Solubility data for the drug substance covering the pH range;
  - b. Detailed description of the dissolution test being proposed for the evaluation of your proposed drug product and the developmental parameters used to select the proposed dissolution method as the optimal test for the proposed product (*i.e., selection of the equipment/ apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.*). Include the data supporting the selection of the type and amount of (b) (4). The testing conditions used for each test should be clearly specified. The dissolution profile should be complete (*i.e., (b) (4) minutes*) and cover at least (b) (4)% of drug release of the label amount or whenever a plateau (*i.e., no increase over 3 consecutive time-points*) is reached. We recommend that at least twelve samples be used per testing variable;
  - c. Provide the complete dissolution profile data (*individual, mean, SD, profiles*). The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*); and
  - d. Include the complete dissolution data for the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as the supportive validation data for the dissolution method (*i.e., method robustness, etc.*) and analytical method (*precision, accuracy, linearity, stability, etc.*).

2. Your NDA submission only included the dissolution-stability data for the (b) (4) minutes time point. Submit the complete dissolution profile (b) (4) data for the stability registration batches. If you have not collected dissolution profile data at all the time points, please start immediately collecting it for the stability batches and submit it to FDA as soon as becomes available.
3. The analytical method validation report “METHVAL-0132-R-A-02 Addendum” for the dissolution test mentioned in section 3.2.P.5.3 could not be located. Submit this report or indicate where the report is located in your NDA.

If you have any questions, call Yvonne Knight, Regulatory Project Manager, at (301) 796-2133.

Sincerely,

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.  
Acting Division Director  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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RAMESH K SOOD  
10/01/2013



NDA 205874

**NDA ACKNOWLEDGMENT**

Keryx Biopharmaceuticals, Inc.  
Attention: James Oliviero, CFA  
Chief Financial Officer  
750 Lexington Avenue, 20<sup>th</sup> Floor  
New York, NY 10022

Dear Mr. Oliviero:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: KRX-0502 (ferric citrate coordination complex) (b) (4) 1 g

Date of Application: August 7, 2013

Date of Receipt: August 7, 2013

Our Reference Number: NDA 205874

Please note that this letter supersedes our previous acknowledgement letter that was dated August 23, 2013.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 6, 2013, in accordance with 21 CFR 314.101(a).

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

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

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the

fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

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

If you have any questions, please contact:

Russell Fortney  
Regulatory Health Project Manager  
301-796-1068

Sincerely,

*{See appended electronic signature page}*

Edward Fromm, R.Ph., RAC  
Chief, Project Management Staff  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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EDWARD J FROMM  
09/04/2013



NDA 205874

**NDA ACKNOWLEDGMENT**

Keryx Biopharmaceuticals, Inc.  
Attention: James Oliviero, CFA  
Chief Financial Officer  
750 Lexington Avenue, 20<sup>th</sup> Floor  
New York, NY 10022

Dear Mr. Oliviero:

We have received your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: KRX-0502 (ferric citrate coordination complex) (b)(4) 1g

Date of Application:

Date of Receipt: August 7, 2013

Our Reference Number: NDA 205874

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 6, 2013, in accordance with 21 CFR 314.101(a).

The active moiety in KRX-0502 (ferric citrate) is ferric ion (Fe<sup>+++</sup>). This fact precludes KRX-0502 from being a (b)(4)

(b)(4) Your claim that the drug substance, ferric citrate, present in KRX-0502 exists as a coordination complexes is irrelevant in determining whether it is a (b)(4) The drug substance (b)(4)

(b)(4) . No evidence has been provided that (b)(4) You have also stated (b)(4) that the Agency had agreed earlier that ferric citrate was (b)(4)

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

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

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

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

If you have any questions, please contact:

Russell Fortney, R.Ph.  
Regulatory Health Project Manager  
(301) 796-1068

Sincerely,

*{See appended electronic signature page}*

Edward Fromm, R.Ph., RAC  
Chief, Project Management Staff  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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EDWARD J FROMM  
08/23/2013

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/s/  
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MARY GRACE LUBAO  
09/22/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 052868

**MEETING MINUTES**

Keryx Biopharmaceuticals  
Attention: Robert Niecestro, Ph.D  
Regulatory Consultant to Keryx  
750 Lexington Ave. 20<sup>th</sup> floor  
New York, NY 10022

Dear Dr. Niecestro:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ferric citrate.

We also refer to the meeting between representatives of your firm and the FDA on March 5, 2013. The purpose of the meeting was to discuss the top line results of your study KRX-0502-304.

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

If you have any questions, please call Michael Monteleone, Regulatory Project Manager at (301) 796-1952.

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, MD, PhD  
Director  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** March 5, 2013; 10:30-12:00 PM  
**Meeting Location:** FDA White Oak Campus, Building 22 Room 1417

**Application Number:** IND 052868  
**Product Name:** ferric citrate  
**Indication:** Treatment of hyperphosphatemia in patients with End-Stage Renal Disease  
**Sponsor/Applicant Name:** Keryx

**Meeting Chair:** Norman Stockbridge, MD, PhD  
**Meeting Recorder:** Michael Monteleone, MS, RAC

**FDA ATTENDEES**

*Division of Cardiovascular and Renal Products*

Norman Stockbridge, MD, PhD	Director
Aliza Thompson, MD	Clinical Team Leader
Nancy Xu, MD	Clinical Reviewer
Melanie Blank, MD	Clinical Reviewer
Gail Moreschi, MD	Clinical Reviewer
Shen Xiao, MD	Clinical Reviewer
Michael Monteleone, MS, RAC	Project Manager
Russell Fortney, RPh	Project Manager
Edward Fromm, RPh, RAC	Chief, Project Management Staff

*Office of Biostatistics, Division of Biometrics I*

Fanhui Kong, PhD	Biostatistician
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*Office of Clinical Pharmacology, Division of Clinical Pharmacology I*

Peter Hinderling, MD	Clinical Pharmacology Reviewer
Ju-Ping Lai, PhD	Clinical Pharmacology Reviewer

Meeting Minutes  
March 5, 2013

**SPONSOR ATTENDEES**

*Keryx*

Ron Bentsur  
James Oliviero  
Robert Niecestro, PhD  
Edward Cullen, PhD  
Pushpa Singh, PhD  
Lesa Gardner, RN  
Enrique Poradosu, PhD  
Anna Kausz, MD

Chief Executive Officer  
Chief Financial Officer  
Regulatory Consultant  
VP Pre-Clinical and Clinical Development  
VP Quality and CMC

(b) (4)

*Vanderbilt University*

Julie Lewis, MD  
Jamie Dwyer, MD  
Mohammed Sika, PhD

Study Chair of KRX-0502-304  
Study Chair DSMC

## 1.0 BACKGROUND

The Sponsor, Keryx Biopharmaceuticals, Inc., is developing KRX-0502 (ferric citrate) for the treatment of hyperphosphatemia in patients (b) (4). On February 4, 2013, the Sponsor requested a meeting to discuss the topline results of their study KRX-0502-304. The Sponsor's request was granted. Prior to the meeting, the sponsor provided a copy of their presentation to the Division [see attached]. The Division met with the Sponsor on March 5, 2013; the minutes of that meeting follow.

## 2. DISCUSSION

After introductions, the Sponsor began their presentation (see attached slides on hyperphosphatemia, the design of the trial, and topline efficacy and safety findings).

### Trial design and conduct:

The Division noted that, as presented, it was difficult to account for study subjects. The Sponsor explained that there were three populations - a safety population, a full analysis population and an efficacy population. The Sponsor also indicated that 4 subjects switched treatment groups during the course of the study. The Sponsor agreed to provide a clear accounting of subjects in the NDA.

The Sponsor's strategy of excluding subjects intolerant of the active control from enrollment was discussed. It was noted that it would be difficult to draw conclusions about relative tolerability (study drug vs. active control) because of this exclusion criterion.

The Division advised the sponsor to include in their NDA a clear description of the flow of information in the trial (among the sponsor, DSMC, and others involved in the management of the trial), along with information on blinding status. The Division also asked the sponsor to submit meeting minutes and copies of any communications between groups involved in the management of the trial (e.g., sponsor, steering committee, DSMC).

### Effects on use of IV iron and ESAs and iron parameters:

The sponsor reported that subjects on study drug received less IV iron and ESA than the active control. (b) (4) Dr. Thompson questioned the clinical significance of the findings on ESA usage. (b) (4)

An early rise and subsequent plateau in TSAT and ferritin levels was noted in the ferric citrate arm. The sponsor hypothesized that the body may be better able to self-regulate iron levels when iron is administered via the GI track as opposed to IV. The Division encouraged the sponsor to consider changes in IV iron administration as a possible explanation for the finding.

The Division asked about the difference in the incidence of patients with serum ferritin >1500 ng/ml in the two treatment arms and the adjudication committee findings (see slide

52). The Sponsor commented that IV iron was allowed per protocol if serum ferritin was less than 1000 ng/ml. Measurements were performed monthly and a given subject could receive a fair amount of IV iron over the course of a month. The Sponsor also noted that because centers had different thresholds for administering IV iron in non-study subjects, some study subjects were mistakenly given IV iron per the center's procedure and in violation of the study protocol.

The Division asked if the Sponsor thought they could define an 'ideal' TSAT/ferritin based stopping rule for IV iron administration. The Sponsor presented a backup slide [attached] which showed wide variability across study sites in TSAT- and ferritin- based stopping rules for administering IV iron, illustrating a general lack of consensus.

The Division asked the sponsor to provide analyses showing the distribution of changes in ferritin and other iron-related laboratory parameters

Drug-Drug interactions:

The sponsor's Drug-Drug Interaction studies were discussed. The Sponsor explained that the *in vitro* screening studies are ongoing. The Division commented that at some point *in vivo* studies may be needed to address false negatives. The Sponsor responded that, thus far, the pattern seems to be consistent with the class and that prescribing information for other members of the class includes instructions for minimizing such interactions. The Division advised the sponsor to send in the DDI study report for comment.

Other:

The Sponsor asked if the Division would be willing to offer further input on analyses/findings as they become available. The Division replied that it would be unable to maintain a running dialog with the Sponsor as they put together their NDA, but that if the sponsor had specific questions, the Division would try to provide a response.

Priority review:

The Sponsor asked about a Priority review. The Division commented that such decisions are made at filing, but that a Priority review did not seem likely.

## **OTHER COMMENTS**

### **PREA PEDIATRIC STUDY PLAN**

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at [Pedsdrugs@fda.hhs.gov](mailto:Pedsdrugs@fda.hhs.gov).

### **PRESCRIBING INFORMATION**

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

### **MANUFACTURING FACILITIES**

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

### **OFFICE OF SCIENTIFIC INVESTIGATIONS**

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

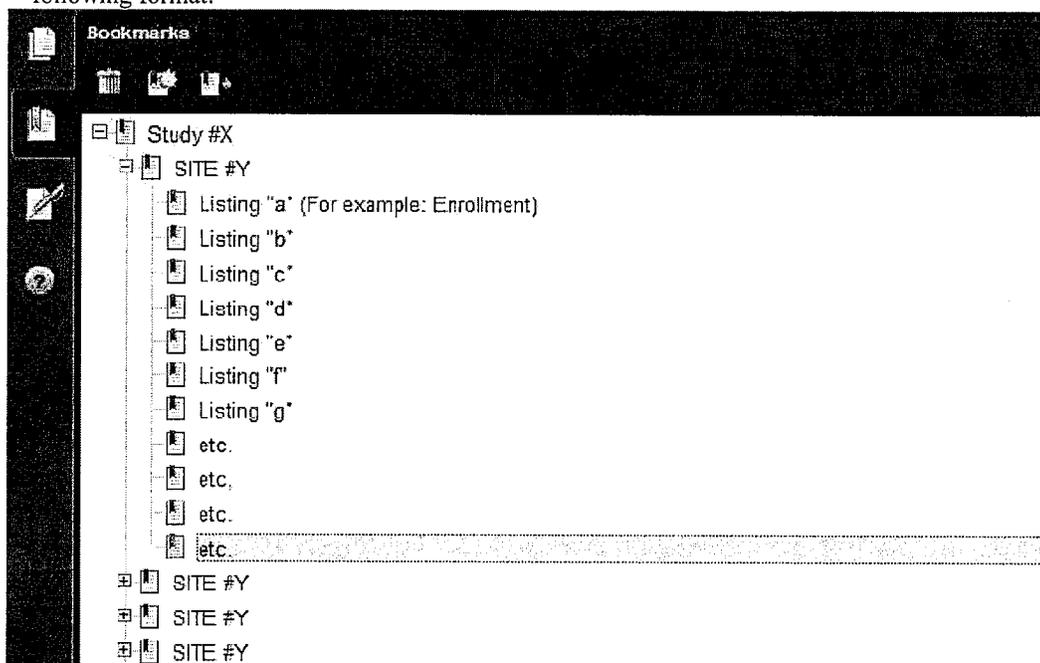
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

- I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**
1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:
    - a. Site number
    - b. Principal investigator
    - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
    - d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
  2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:
    - a. Number of subjects screened for each site by site
    - b. Number of subjects randomized for each site by site
    - c. Number of subjects treated who prematurely discontinued for each site by site
  3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
    - a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
    - b. Name, address and contact information of all CROs used in the conduct of the clinical trials

- c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
  - d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)
4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).
  5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

## II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data (“line”) listings. For each site provide line listings for:
  - a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
  - b. Subject listing for treatment assignment (randomization)
  - c. Subject listing of drop-outs and subjects that discontinued with date and reason
  - d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
  - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
  - f. By subject listing, of AEs, SAEs, deaths and dates
  - g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
  - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
  - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
  - j. By subject listing, of laboratory tests performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



**III. Request for Site Level Dataset:**

OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Attachment 1, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

## Attachment 1

### Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

#### INTRODUCTION

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

#### DESCRIPTION OF THE SUMMARY LEVEL CLINICAL SITE DATASET

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

#### **Site-Specific Efficacy Results**

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)
- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, “TRTEFFR.”

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the “endpoint” plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (\*.xpt).

Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., not limited to only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount (\$USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount (\$USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parties. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	INITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table I)

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLIDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

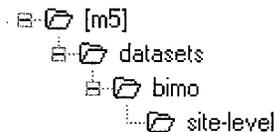
## Attachment 2

### Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clnsite.xpt.”

DSI Pre-NDA Request Item <sup>1</sup>	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study  (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

<sup>1</sup> Please see the OSI Pre-NDA Request document for a full description of requested data files

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References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1  
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page  
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: [ESUB@fda.hhs.gov](mailto:ESUB@fda.hhs.gov)

#### **4.0 ATTACHMENTS AND HANDOUTS**

Sponsor's presentation

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/s/  
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NORMAN L STOCKBRIDGE  
03/22/2013



IND 052868

**MEETING MINUTES**

Keryx Biopharmaceuticals  
Attention: Robert Niecestro, Ph.D  
Regulatory Consultant to Keryx  
750 Lexington Ave. 20<sup>th</sup> floor  
New York, NY 10022

Dear Dr. Niecestro:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ferric citrate.

We also refer to the meeting between representatives of your firm and the FDA on September 19, 2012. The purpose of the meeting was to discuss nonclinical and clinical pharmacology aspects of your planned NDA submission.

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

If you have any questions, please call Michael Monteleone, Regulatory Project Manager at (301) 796-1952.

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, MD, PhD  
Director  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** September 19, 2012; 12:00-1:00 PM  
**Meeting Location:** FDA White Oak Campus, Building 22 Room 1419

**Application Number:** IND 052868  
**Product Name:** ferric citrate  
**Indication:** Treatment of hyperphosphatemia in patients with End-Stage Renal Disease  
**Sponsor/Applicant Name:** Keryx

**Meeting Chair:** Norman Stockbridge, MD, PhD  
**Meeting Recorder:** Michael Monteleone, MS, RAC

**FDA ATTENDEES**

*Division of Cardiovascular and Renal Products*

Norman Stockbridge, MD, PhD	Director
Nancy Xu, MD	Clinical Reviewer
Albert Defelice, PhD	Non-Clinical, Team Leader
Thomas Papoian, PhD	Non-Clinical, Team Leader
Rama Dwivedi, PhD	Pharmacologist
Edward Fromm, RPh, RAC	Chief, Project Management Staff
Michael Monteleone, MS, RAC	Project Manager

*Division of Biometrics, Division of Biometrics I*

Fanhui Kong, PhD	Biostatistician
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*Office of Clinical Pharmacology, Division of Clinical Pharmacology I*

Rajnikanth Madabushi, PhD	Clinical Pharmacology, Team Leader
Peter Hinderling, MD, PhD	Clinical Pharmacology Reviewer

**SPONSOR ATTENDEES**

*Keryx*

Ron Bentsur

James Oliviero

Robert Niecestro, PhD

Edward Cullen, PhD

Madlen Malinowski

John Dillberger, DVM, PhD

Chief Executive Officer

Chief Financial Officer

Regulatory Consultant

Vice-President Pre-Clinical and  
Clinical Development

Regulatory Affairs

Toxicology Consultant

(b) (4)

## 1.0 BACKGROUND

The Sponsor, Keryx Biopharmaceuticals, Inc. is developing KRX-0502 (ferric citrate) for the treatment of hyperphosphatemia in patients with End-Stage Renal Disease. On July 12, 2012 the sponsor requested a meeting to discuss the nonclinical and clinical pharmacology progress to date, the proposed nonclinical and clinical pharmacology program to support an NDA submission, and the structure and format of the clinical portion of the NDA, including the Integrated Summary of Effectiveness and Integrated Safety Summary. The Division granted the sponsor's request for a meeting on August 3, 2012, and provided preliminary comments to the sponsor questions on September 14, 2012. Prior to the meeting, the Division also conveyed comments regarding submission of an NDA pursuant to 505(b)(2), those comments are included here for the record. The Division met with the sponsor on September 19, 2012; the minutes of that meeting follow.

## 2. DISCUSSION

During the meeting the sponsor referred to a short handout, [see Attachments].

Prior to meeting with the sponsor, the Division conveyed the following general comments regarding submission of an NDA pursuant to 505(b)(2) as well as specific comments under questions 4 and 5.

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry Applications Covered by Section 505(b)(2) (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate. We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature.

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's determination that the drug was not discontinued for reasons of safety or effectiveness.

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

**Question 1:** *Based on the reports for chronic toxicity studies of ferric citrate that were submitted to IND 052868, the availability of publications describing lifetime carcinogenicity studies of ferric citrate and other iron-based compounds, and the life expectancy of three to five years for ESRD patients on dialysis, Keryx believes that additional carcinogenicity studies of ferric citrate should not be required for ESRD patients on dialysis. Does the FDA agree?*

**Preliminary Response:** Yes, we agree that no further studies are needed, based on the availability of publications describing lifetime rodent carcinogenicity studies of ferric citrate and other iron-based compounds.

**Discussion during the meeting:** None

**Question 2:** *Keryx believes that additional reproductive toxicology studies should not be required for ESRD patients on dialysis. Does the FDA agree?*

**Preliminary Response:** Yes, we agree, based on the availability of published reproductive and developmental toxicity studies and the limited transplacental transfer of iron in animals.

**Discussion during the meeting:** None

**Question 3:** *Keryx believes that no additional safety pharmacology studies should be required in the NDA. Does the FDA agree?*

**Preliminary Response:** Yes, we agree, based on the limited amount of iron absorption after 28 days of treatment in animals.

**Discussion during the meeting:** None

**Question 4:** *Keryx proposes to use modified text from the Package Insert for Omnicef (cefdinir) to address the interaction in the Package Insert for ferric citrate: "Iron preparations have been shown to inhibit the absorption of cefdinir when administered simultaneously. If treatment with cefdinir is required, ferric citrate and cefdinir administration should be separated by at least 2 hours." Is this acceptable to the FDA?*

**Preliminary Response:** Yes, your approach to drugs that have reduced bioavailability in the presence of iron containing compounds is, as a whole, reasonable. The separation by 2 hours to mitigate the interaction depends upon the Tmax of the concomitantly administered drugs and the gastric emptying time of ferric citrate. Since both the products are generally administered with food, separation of the two drugs may not be practically feasible.

Please note that the Sinemet (IR and CR) Package Insert of 1-31-2011 states: "Iron salts may reduce the bioavailability of levodopa and carbidopa. The clinical relevance is unclear" This statement is different from the one you cite: "(b) (4)

Pre-Meeting comment sent via email: Whether this proposal constitutes reliance on our finding of safety and/or effectiveness for a listed drug (Omnicef) is a review issue. Several factors may influence this determination. As such, it is premature for us to respond to this question at this time. Please note, however, that using another sponsor's product labeling information to address a potential interaction between your product and another without right of reference may, in certain instances, constitute reliance on that product. Addressing these drug interactions based solely on information/data you own or to which you have right of reference, however, would eliminate concerns with reliance on our finding of safety and/or effectiveness for a listed drug.

**Discussion during the meeting:** See Question 5.

**Question 5:** *Keryx believes that the currently available package of drug-drug interaction information, and the proposed approach of applying information from the literature, including available Package Inserts, to the ferric citrate Package Insert is sufficient for the NDA for ESRD patients on dialysis. Does the FDA agree?*

**Preliminary Response:** Your currently available *in vitro* package of drug-drug interactions is not sufficient. The approach you have taken is based on the probability of

co-administration. However, given the polypharmacy conditions encountered in the target population for KRX-0502 this approach may miss important interactions. We recommend that you use a rational *in vitro* approach which is based on the notion that the probability of complex formation with reduced bioavailability depends on the structure of the non-iron compounds. Chelates with Fe<sup>++</sup> or Fe<sup>+++</sup> are formed with compounds for example containing -SH, =NH, -OH, -OPO<sub>3</sub>H or >C=O groups. Orally administered drugs with and without these and possibly additional structural characteristics should be screened *in vitro* and the need for an *in vivo* study determined. The *in vitro* experiments should be performed at pH 1.2, 4.5 and 6.8.

Pre-Meeting comment sent via email: Whether the proposal to apply information from the literature, including available package inserts, constitutes reliance on our finding of safety and/or effectiveness for a listed drug or drugs is a review issue. Several factors may influence this determination. As such, it is premature for us to respond to this question at this time. Please note, however, that using another sponsor's product labeling information to address a potential interaction between your product and another without right of reference may, in certain instances, constitute reliance on that product. Addressing these drug interactions based solely on information/data you own or to which you have right of reference, however, would eliminate concerns with reliance on our finding of safety and/or effectiveness for a listed drug

#### **Discussion during the meeting:**

There was some discussion regarding the sponsor's planned drug-drug interactions (DDI) package. The sponsor presented a number of examples of drugs they have studied and the outcome, positive and negative, as well as potential articles for future tests. The sponsor commented that not all drugs were soluble and so it is not feasible to look for precipitate in those; Dr. Stockbridge agreed.

Dr. Hinderling recommended that the sponsor explore a QSAR guided strategy that selects the compounds to be tested based on the presence or absence of structures expected to form chelates with iron. Of course with both approaches, the predictability of the *in vitro* experiments to the *in vivo* situation must be demonstrated including validation (true/false positives, true/false negatives). Dr. Hinderling commented that the table in the sponsor's 3<sup>rd</sup> slide shows no precipitation for 7 of the tested drugs despite the presence of at least one structure known to enable chelation in the presence of ferric citrate. Only 3 compounds benserazide, L-DOPA and cefdinir in the presence of ferric citrate show precipitation in agreement with previous *in vivo* findings. These results indicate that the structural requirements of co-administered drugs to induce chelation with ferric citrate may be more complex and suggest that more than just the presence of a single enabling structure may be needed. Therefore, the sponsor should test the QSAR approach by selecting those drugs for *in vitro* testing that were shown to have a reduced bioavailability when co-administered with iron *in vivo*.

Dr. Hinderling asked the sponsor to consider that chelation does not only impact the bioavailability of co-administered drugs but also reduces the bioavailability of ferric

citrate. The loss of iron and co-administered drug from precipitation in the *in vitro* studies can be quantified.

The Division offered to comment on the studies the sponsor may want to perform. The sponsor indicated that they will provide an outline of their *in vitro* studies.

Dr. Xu discussed with the sponsor the apparent increased GI absorption of aluminum in the presence of citrate as suggested by the medical literature. The sponsor commented that they were examining the potential of ferric citrate to increase exposure to aluminum. The sponsor confirmed that exposure to aluminum is measured in the clinical trials and the results will be included in the report on study 304.

**Question 6:** *Are the proposed studies adequate to satisfy the requirements for Pediatric Exclusivity and a Written Request for Keryx's ferric citrate?*

**Preliminary Response:** The studies performed under a Written Request should be designed to provide the information that health care providers or parents need to use the drug appropriately in the pediatric population. Insufficient information has been submitted for us to determine the type of data (i.e., efficacy, safety, dose-response) that would need to be obtained from pediatric studies. Hence, at this time, we cannot provide further comment on the adequacy of your proposed pediatric development program.

**Discussion during the meeting:** The sponsor advised that they have some data that suggest that neonatal rats are particularly sensitive to iron toxicity (see Slide #6 of sponsor's presentation). Dr. Papoian commented that the relevant question was how does the rat model relate to humans. Of particular interest is when an infant human begins to respond as an adult, i.e. what is the window of vulnerability. The sponsor commented they would need to follow-up on this. Dr. Xu commented that iron storage may be different between juveniles and adults. Dr. Papoian asked if the sponsor intended to look at serum phosphorus and bones to which the sponsor responded that they will look at serum phosphorus as part of their standard clinical chemical studies and will also look at bones.

Regarding the pediatric plan, Dr. Stockbridge commented that ferric citrate is not receptor mediated and likely to bind phosphate in pediatric patients. The objective of a pediatric program should focus mostly on defining appropriate dosing instructions. The sponsor was advised to continue to work with the Division on their pediatric development plan.

**Question 7:** *Is our definition of an abbreviated clinical study report acceptable to the FDA?*

**Preliminary Response:** The abbreviated clinical study report should also contain disposition data.

**Discussion during the meeting:** The Sponsor agreed.

**Question 8:** *Is our proposal to submit abbreviated clinical study reports in the NDA for the following completed supportive clinical trials: KRX-0502-202 (Israel), Univ. of Mich. 1, Univ. of Mich. 2, OLE in Taiwan, GBA4-4 (completed supportive trial in subjects with chronic kidney disease not undergoing dialysis) and for the following ongoing clinical trials: KRX-0502-307 (safety data to be integrated into integrated safety database), GBA 4-5 (long-term safety trials in subjects with ESRD in Japan), GBA4-6 (long-term safety trial in subjects with ESRD in Japan), and GBA 4-7 (long-term safety trial in subjects with chronic kidney disease not undergoing dialysis in Japan) acceptable to the FDA?*

**Preliminary Response:** Yes. See also our response to Question 7.

**Discussion during the meeting:** None.

**Question 9:** *Is our proposal to identify three clinical trials as “adequate and well-controlled” (Keryx Studies KRX-0502-304 and KRX-0502-305 conducted under Special Protocol Assessment and PBB00101) to support the filing of an NDA acceptable to the FDA?*

**Preliminary Response:** The data, as described, would be sufficient to support filing of an NDA.

**Discussion during the meeting:** None.

**Question 10:** *Is our proposal to integrate safety data from the five clinical trials conducted under 052868 sponsored by either Keryx or Panion (Keryx Studies KRX-0502-201, KRX-0502-304, KRX-0502-305, KRX-0502-307 and PBB00101) acceptable to the FDA?*

**Preliminary Response:** Yes.

**Discussion during the meeting:** None.

**Question 11:** *Is our proposal to tabulate the safety results from the 12 other clinical trials in the Integrated Safety Summary acceptable to the FDA?*

**Preliminary Response:** Yes. You should also submit the datasets needed to generate these tables (see Response to Question 16).

**Discussion during the meeting:** None.

**Question 12:** *Is the proposed subject exposure data in the proposed integrated safety database based on the five clinical trials conducted under IND 052868; and is the overall exposure across all 17 clinical trials, adequate to file an NDA?*

**Preliminary Response:** Yes.

**Discussion during the meeting:** None.

**Question 13:** *Is the proposed cut-off date for the inclusion of safety data from ongoing clinical trials acceptable to the FDA?*

**Preliminary Response:** Yes.

**Discussion during the meeting:** None.

**Question 14:** *Keryx would like to propose that we submit subject narratives for all subjects that died in Keryx Study KRX-0502-304, all serious adverse events that are related to study drug as determined by either the Independent Medical Monitors/DSMC or Principal Investigators, and all subjects that discontinued due to an adverse event. Is this acceptable to the FDA?*

**Preliminary Response:** Yes. You should also submit these narratives for subjects enrolled in other studies. Please also see our response to Question 15.

**Discussion during the meeting:** The sponsor asked to clarify that the Division wanted narratives for all subjects; the Division confirmed.

**Question 15:** *Is it acceptable to the FDA for Keryx to include these subject narratives in both the final clinical study report for Keryx Study KRX-0502-304 and in the Integrated Safety Summary section of the NDA?*

**Preliminary Response:** Yes. Please also submit these narratives for other studies. In addition, for all studies, you should submit narratives for subjects who were discontinued from therapy because of elevated levels of iron-related parameters. Among other things, these narratives should address whether subjects experienced any clinical manifestations/adverse outcomes associated with high iron levels.

**Discussion during the meeting:** The sponsor reiterated that they plan to submit narratives for subjects with serum ferritin >1500 ng/mL. Dr. Xu indicated that to understand the implication of oral iron administration via ferric citrate in those with higher baseline iron indices (e.g. serum ferritin >800 ng/mL and TSAT >30%), additional narratives may be requested during the NDA review. The sponsor attributed the high ferritin levels of >1500 ng/mL to IV iron administration during the trial and stated that they intended to submit the IV iron administration protocols from each site in the NDA, given the variability in protocols. Dr. Xu commented it would also be helpful to have the dose and timing of the parenterally administered iron included as parameters in a dataset.

Additional comments for dataset(s) are as follows.

To facilitate review, please provide a dataset containing all subjects treated with ferric citrate or placebo, with one record per subject and the following information: the unique subject id, study treatment (ferric citrate or placebo) received, first study treatment date, last study treatment date, arithmetic mean dose of study treatment per day, maximum dose of study treatment per day, type of parenteral iron, route of parenteral iron administration, the arithmetic mean dose per week of parenterally administered iron prior to study treatment administration (in total milligram per week), the arithmetic mean dose

per week of parenterally administered iron while on study treatment (in total milligram per week), cumulative dose of parenteral iron over the entire study treatment phase (52 weeks), the arithmetic mean dose per week of erythropoietin prior to initiating study treatment, the arithmetic mean dose per week of erythropoietin while on study treatment, cumulative dose of erythropoietin over the entire study treatment (52 weeks), baseline ferritin, baseline transferrin saturation, indicator for any increase in ferritin level on treatment as compared to the baseline, indicator for any increase in transferrin saturation on-treatment as compared to baseline, and indicator for any infection event during study drug treatment.

Please also provide a dataset with all subjects who had infection event(s) upon starting study drug. Please provide one record per infection event and the following information: the unique subject id, study treatment (ferric citrate vs. placebo) received, type of infection, infection event start date, infection resolution date, infection event days from first study treatment dose date (infection start date minus study treatment first dose date +1), infection event days from the last parenterally administered iron dose, indicator for ferritin >800 ng/dL on-treatment, indicator for ferritin >1000 ng/mL on-treatment, indicator for ferritin >1500 ng/mL on-treatment.

**Question 16:** *Is this approach for the presentation of the clinical data, datasets and SAS datasets in the NDA acceptable to the FDA?*

**Preliminary Response:** Yes. In addition, please submit;

- all datasets and SAS code used to generate your main tables and figures for your pivotal studies and the ISS,
- a table that lists and hyperlinks to: (1) all of the main tables and figures in your pivotal trials and Integrated Safety Summary; (2) the SAS code used to generate the table or figure; and (3) the datasets used to generate the table or figure,
- CRFs for subjects who experience any of the events listed in Questions 14 and 15.

**Discussion during the meeting:** None.

**Question 17:** *Does Keryx need to file a paper copy of the NDA with the FDA?*

**Preliminary Response:** No, paper copies are not submitted for electronically submitted NDAs.

**Discussion during the meeting:** None.

#### **Additional Comments and Questions:**

#### **Statistics**

1. In response to your question, “Is Amendment 4 acceptable for the secondary endpoints to the FDA as the final SAP for Keryx Study KRX-0502-304?”: We agree.

### **Clinical Pharmacology**

1. What clinical pharmacology studies will you submit as part of the NDA and what are the major findings?
2. What do you think are the relevant clinical pharmacology issues with KRX0502?

### **Clinical**

1. Please submit as part of your NDA the Independent Medical Monitor/DSMC meeting minutes for studies KRX-0502-304 and KRX-0502-305, as well as any correspondence between these groups and Keryx/those overseeing the conduct of the trials.
2. We would like further information on the analyses that will be done to address potential risks associated with the absorption of iron from your product.

### **Additional discussion during the meeting:**

Dr. Hinderling asked the sponsor for information on potential risks caused by the citrate portion of their drug. The sponsor commented that because it is approved for use in food; they have viewed it as benign and not looked at it much.

Regarding 505(b)(2) issues, the Division offered to work with the sponsor on any questions they might have as the prepare for NDA submission.

### **OTHER COMMENTS**

#### **PREA PEDIATRIC STUDY PLAN**

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at [Pedsdrugs@fda.hhs.gov](mailto:Pedsdrugs@fda.hhs.gov).

#### **PRESCRIBING INFORMATION**

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

**MANUFACTURING FACILITIES**

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

#### 4.0 ATTACHMENTS AND HANDOUTS

Sponsor's presentation

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/s/  
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NORMAN L STOCKBRIDGE  
10/03/2012

Meeting Minutes

**Date:** May 4, 2009  
**Application:** IND 52,868  
**Sponsor:** Keryx Biopharmaceuticals  
**Meeting Purpose:** End of Phase 2  
**Meeting Type:** B

**FDA Attendees:**

Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products
Ellis Unger, M.D.	Deputy Director (acting), Office of Drug Evaluation-I
Melanie Blank, M.D.	Medical Reviewer
Xavier Joseph, Ph.D.	Pharmacology Reviewer
Charles Resnick, Ph.D.	Pharmacology Team Leader
Islam Younis, Ph.D.	Clinical Pharmacologist
Angelica Dorantes, Ph.D.	Clinical Pharmacology Team Leader
Russell Fortney	Regulatory Project Manager
Lori Anne Wachter, R.N., B.S.N.	Regulatory Project Manager

**Attendees:**

Michael Tarnok	Acting Chairman and CEO, Keryx (b) (4)
Edward Cullen, PhD	Vice-President Pre-Clinical and Clinical Development, Keryx
Nicole Michaelson	Associate Director, Regulatory Affairs, Keryx
Carolyn Connelly	Director, Clinical and Regulatory Affairs, Keryx
Julie Lewis, MD	Vanderbilt University: Professor of Medicine
Mark Koury, MD	Vanderbilt University: Professor of Medicine (Hematology/Oncology)

(b) (4)

**Background:**

The sponsor is developing Zerenex (ferric citrate) to control (b) (4) serum phosphorous in chronic kidney disease patients on hemodialysis. The sponsor requested this meeting to update the Agency on the current clinical and nonclinical development status of Zerenex and to seek the Agency's guidance on a path forward in filing a NDA. Preliminary responses to the submitted questions were conveyed to the sponsor prior to the meeting and are copied below, followed by any discussion that took place during the meeting.

**Meeting:**

The following Questions were addressed:

**Non-clinical Questions**

**Question 1**

Keryx submitted the protocols for the 6-month chronic toxicity study in rats and 42-week chronic toxicity study in dogs to the FDA on March 12, 2009 (IND Serial Submission 0042).

*Does the FDA have any comments on these protocols?*

**Preliminary FDA Response:** The doses proposed for chronic toxicity studies in rats and dogs are not acceptable.

*Rat Study* – Because no dose-limiting toxicity was observed in the 90-day rat study at doses up to 2800 mg/kg/day, we see no reason to use a lower maximum dose level for the 6-month study. For the 6-month study, we recommend the same doses used for the 3-month study (0, 500, 1400 and 2800 mg/kg/day).

*Dog Study* – The proposed high dose of 1200 mg/kg/day for the 42-week study did not produce any notable toxicity in the 16-week study. We recommend dose levels of 0, 500, 1000 and 2000 mg/kg/day for the chronic dog study.

**Additional discussion during meeting:** Japan Tobacco is the sponsor of the 6-month rat and the 42-week dog studies which are already in progress. Keryx proposed additional studies to evaluate the 2800-mg/kg/day dose in rats and the 2000-mg/kg/day dose in dogs. Dr. Resnick said that it would be acceptable for these single dose level studies (which should include controls) to be run in parallel with the other studies.

**Question 2**

Keryx is planning to initiate the two ten-week efficacy assessment clinical trials in approximately September 2009.

*Given the fact that the 90-day rat and 16-week dog final reports have been submitted to the IND, Is this acceptable to the Agency?*

**Preliminary FDA Response:** This is acceptable.

**Additional discussion during meeting:** No additional discussion.

**Question 3**

Is dosing patients up to 10 weeks in the efficacy treatment period with a daily dose not exceeding 12 gram per day acceptable to the Agency?

**Preliminary FDA Response:** This is acceptable.

**Additional discussion during Meeting:** No additional discussion.

**Question 4**

Is it acceptable to the Agency for Keryx to initiate the long-term human exposure (exposure to KRX-0502 (ferric citrate) > 12 weeks) clinical trial in late October 2009 with the in-life portion of the 6-month rat

toxicity trial completed and approximately 75% of the dosing in the 42-week dog toxicity study completed?

**Preliminary FDA Response:** The clinical trial should not be initiated until necropsies of both the rats, dogs in the above noted studies are completed, and the gross pathology and clinical pathology examinations provide no evidence of adverse effect. Should these exams provide cause for concern, initiation of the clinical trial should be delayed until all of the animal data are considered and risks to clinical trial participants are determined to be acceptable.

**Additional discussion during meeting:** The sponsor agreed to submit interim reports of the 6-month rat and 42-week dog toxicity studies, in-life, necropsy and related histology findings, before proceeding with the clinical trial.

### Iron Monitoring Questions

#### **Question 1**

Does the Agency agree with Keryx's plan to exclude patients with serum ferritin concentrations over 1000 ng/mL or transferrin saturations over 50%?

**Preliminary FDA Response:** We agree.

**Additional discussion during meeting:** No additional discussion.

#### **Question 2**

Does the Agency agree with Keryx's plan regarding the use of intravenous iron in the proposed Phase III clinical trials?

**Preliminary FDA Response:** We agree.

**Additional discussion during meeting:** No additional discussion.

#### **Question 3**

Iron studies including serum iron, ferritin, TSAT, and TIBC will be drawn during the screening period, at the end of the washout period, every two weeks during the ten-week efficacy treatment period, then monthly thereafter during the long-term extension period.

*Is this plan acceptable to the Agency?*

**Preliminary FDA Response:** Yes.

**Additional discussion during meeting:** No additional discussion.

#### **Question 4**

Our Independent Medical Monitor, [REDACTED] (b) (6) of Vanderbilt University, will be monitoring all iron parameters in "real-time" and on an ongoing basis for each patient enrolled in the Phase III clinical trials.

*Does the Agency have any additional suggestion regarding the monitoring of the patients for potential iron absorption or overload beyond those that have already been proposed by Keryx?*

**Preliminary FDA Response:** Yes. Because we have concerns about hepatotoxicity from the nonclinical studies, we recommend that you monitor the subjects who will be exposed to the study drug for over 6 months for changes in serum albumin, prothrombin time and partial thromboplastin time.

**Additional discussion during meeting:** Serum albumin and liver function tests are drawn monthly on all dialysis patients via the patient's dialysis access. In order to monitor prothrombin time (PT) and partial thromboplastin time (PTT), a peripheral blood draw is required and can be difficult to obtain on a hemodialysis patient. Therefore, it was agreed that PT and PTT monitoring would be performed at baseline and every three months thereafter during the long-term study.

### Clinical Questions

#### **Question 1**

Following a two-week washout period in the proposed two Phase III clinical trials, is baseline to endpoint change at week 10 for serum phosphorus sufficient for the primary efficacy assessment?

**Preliminary FDA Response:** We recommend that you combine and redesign your studies so that you have:

- An early 10 week fixed dose-ranging study where you can assess the starting dose and time to titration, followed by:
- A 52-week titration effect study where you would enroll additional subjects who would not necessarily have to go through the dose-ranging part of the study for conducting your safety assessment, followed by:
- A final post-52-week randomized withdrawal study to assess the long-term efficacy.

**Additional discussion during meeting:** The following was agreed upon:

The ten-week trial will be a fixed-dose trial of approximately 80 subjects, all treated with ferric citrate. It will include a four-week wash-out period followed by the dose-ranging period, for a total of 14 weeks. The goal of the wash-out period is to achieve a serum phosphate level between 6-8 or 9 mg/dL at baseline.

The duration of the long-term safety trial will be 52 weeks, followed by a four-week randomized withdrawal wash-out period, for a total of 60 weeks. There will be approximately 40 patients on PhosLo and 40 patients on Renvela as a control for safety during the 52-week safety trial. For weeks 52 – 60, subjects on ferric citrate during the trial, will be randomized to either ferric citrate or placebo for four weeks.

#### **Question 2**

It is our belief that most patients will have a serum phosphorus level of approximately 7 to 8 mg/dL after the two-week washout period, and that treatment with ferric citrate will reduce serum phosphorus levels to approximately 5 to 6 mg/dL.

#### **Question 2.1**

Based on our previous discussion with the Agency, the Agency agreed that this would be a clinically significant reduction (Attachment 1-question 1).

*Is this still acceptable to the Agency?*

**Preliminary FDA Response:** While this plan is still acceptable, we recommend that you prolong your washout period to 4 weeks to increase the baseline serum phosphorus levels beyond 7-8 mg/dL for more subjects. We have no objections to adding a provision whereby subjects whose serum phosphorus levels rise to a certain limit (i.e.,  $\geq 10$  mg/dL) would be randomized earlier than the 4 weeks. We believe that this additional washout period would be advantageous to your drug development program.

**Additional discussion during meeting:** The four-week washout was agreed upon.

**Question 2.2**

The Agency recommended that we include patients with serum phosphorus levels  $> 8$  mg/dL in the clinical trials (Attachment 1-question 1). It is anticipated based on the proposed inclusion and exclusion criteria for the Phase III clinical trials that approximately 5 % of the patients in our Phase III clinical program should have serum phosphorus levels  $> 8$  mg/dL after the two-week washout period. Keryx is planning to recruit patients in the clinical trials with a serum phosphorus level  $\geq 6.0$

**Preliminary FDA Response:** Please see answer to Clinical Question 2.1

**Additional discussion during meeting:** The four-week washout period should provide patients with serum phosphate levels  $> 8$  mg/dL in the clinical trial.

**Question 2.3**

The starting dose of KRX-0502 (ferric citrate) will be 4 g/day for patients with a serum phosphorus level after the washout period  $\geq 6.0$  mg/dL  $< 7.5$  mg/dL. For patients with serum phosphorus  $\geq 7.5$  mg/dL, the starting dose will be 2 g with each meal or 6 g/day.

*Is this starting dose for KRX-0502 (ferric citrate) acceptable to the Agency?*

**Preliminary FDA Response:** Please see answer to Clinical Question 1. The doses that you choose to study should be doses that you anticipate will be effective from your phase 2 study experience.

**Additional discussion during meeting:** No additional discussion.

**Question 2.4**

It is our intention to titrate the dose of KRX-0502 (ferric citrate) on a bi-weekly basis to achieve a serum phosphorus level that ranges from 3.5 mg/dL to 5.5 mg/dL.

*Is this acceptable to the Agency?*

**Preliminary FDA Response:** Please see answer to Clinical Question 1. Your titration schedule should be based on the first dose-ranging part of the study. The goal range for serum phosphorus level is acceptable.

**Additional discussion during meeting:** The sponsor will include a dose titration schedule in the protocols.

**Question 3**

The secondary efficacy endpoint will be responder analysis. A responder will be defined as a patient achieving a serum phosphorus level  $\leq 5.5$  mg/dL at week 10.

*Is this plan acceptable to the Agency?*

**Preliminary FDA Response:** Please see answer to Clinical Question 1. We suggest that you you're your primary analyses on short-term efficacy and long term efficacy. When you design your secondary analyses you may want to consider choosing other efficacy variables that could potentially distinguish ferric citrate from other phosphate binders.

**Additional discussion during meeting:** No additional discussion.

**Question 4**

Are our two "pivotal" Phase III clinical trials and proposed long-term exposure program exposing patients for up to 52 weeks to KRX-0502 (ferric citrate) sufficient for filing an NDA?

**Preliminary FDA Response:** Please see answer to Clinical Question 1.

**Additional discussion during meeting:** The two studies the Agency proposed will be sufficient to file an NDA; the withdrawal study will qualify as the second confirmatory study. Both studies must be appropriately powered. Dr. Stockbridge stated that 200 subjects exposed to ferric citrate should provide adequate safety data.

**Question 5**

The Agency has encouraged Keryx to use the to-be marketed formulation, or as close to this version as possible in their Phase III clinical trials. In Studies KRX-0502-303 and KRX-0502-304, we plan to use the marketed formulation (b) (4) produced in two locations. The majority of the patients will be exposed to the marketed formulation produced at commercial scale at our intended commercial manufacturer. The other manufacturer will use comparable systems procedures, specifications, and controls on a smaller scale.

*Does the FDA have any comments?*

**Preliminary FDA Response:** Before we can advise you regarding the equivalence data that would be needed to bridge the clinical trial's products, please provide detail information for the location of the manufacturing sites, manufacturing procedures, batch size, formulation(s), and acceptance criteria. Also, please identify the product that will be used in studies KRX-0502-303 and KRX-0502-304.

**Additional discussion during meeting:** The sponsor proposed to have a separate meeting to discuss CMC issues. Once that meeting has been held, the sponsor agrees to amend the protocol prior to beginning Phase 3 studies.

**Question 6**

For the long-term extension components of Keryx Studies 0502-303 and 0502-304, it is our intention to have these parts of the clinical trial mimic actual patient treatment in a dialysis unit. Therefore, we are planning to draw plasma on a monthly basis, will titrate the dose of KRX-0502 (ferric citrate) according to serum phosphorus levels, and will evaluate iron parameters (ferritin, serum iron, transferrin, and TIBC).

*Is the interval for assessment of plasma chemistry panel in the long-term extension acceptable to the Agency?*

**Preliminary FDA Response:** It is acceptable.

**Additional discussion during meeting:** No additional discussion.

**Question 7**

Is the design of the clinical pharmacology study of <sup>59</sup>Fe-labeled KRX-0502 (ferric citrate), described in the draft protocol synopsis in Attachment 9, acceptable to FDA?

**Preliminary FDA Response:** There is no need to conduct the <sup>59</sup>Fe-labeled KRX-0502 study.

**Additional discussion during meeting:** No additional discussion.

**Question 8**

As discussed previously and agreed upon, Keryx intends to file one of the protocols (KRX-0502-303 or KRX-0502-304) for Special Protocol Assessment.

*Does the Agency have any preference or advice as to which protocol should be submitted for SPA?*

**Preliminary FDA Response:** Please submit both protocols as a Special Protocol Assessment, given our recommendation to completely redesign your phase 3 development program.

**Additional discussion during meeting:** The sponsor will submit both the protocol and the statistical plan for both the short- and long-term studies as a SPA.

**NDA Planning Questions**

**Question 1**

Is this plan for the submission of the NDA and the submission of long-term safety data acceptable to the Agency?

**Preliminary FDA Response:** You will need to submit all of the data from the study(ies) at the time of your NDA submission.

**Additional discussion during meeting:** No additional discussion.

**Question 2**

Keryx is planning to submit the results from the iron (59) clinical trial as part of the NDA submission.

*Is the submission of the results from the iron (59) study in the NDA acceptable to the Agency?*

**Preliminary FDA Response:** Please see answer to Clinical Question 7.

**Additional discussion during meeting:** No additional discussion.

**Additional Preliminary Comments**

- We recommend that you conduct *in vitro* interaction studies between KRX-0502 and all of the concomitant medications typically administered to End Stage Renal Disease patients. The presence of an *in vitro* interaction between KRX-0502 and another drug will necessitate the conduct of an *in vivo* drug-drug interaction study in healthy volunteers.
- You have only provided synopses of the protocols. The brief descriptions in the synopses indicate that the statistical analysis plans are unclear and confusing. Please provide complete and clear statistical analysis plans when you submit the redesigned protocols.

Minutes preparation: *{See appended electronic signature page}*  
Lori Wachter, RN, BSN

Concurrence, Chair: *{See appended electronic signature page}*  
Norman Stockbridge, M.D., Ph.D.

Drafted-L Wachter 5.14.09; Final-LWachter 5.21.09

Reviewed: X. Joseph 5-19-09  
C. Resnick 5-19-09  
E. Unger 5-21-09  
Stockbridge 5/21/09

Linked Applications

Sponsor Name

Drug Name / Subject

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Lori A WACHTER

05/22/2009

NORMAN L STOCKBRIDGE

05/22/2009