CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212832Orig1s000

PRODUCT QUALITY REVIEW(S)

QUALITY ASSESSMENT

Recommendation: As of this review, this 505 (b)(2) NDA is *not* ready for Approval in its present form per 21 CFR 314.125(b)(6).

NDA 212832

OPQ Review #1

Drug Name/Dosage Form	Potassium Phosphates Injection, for intravenous use
Strength	3 mmol Phosphorus and 4.4 mEq Potassium/mL 1. **15 mmol Phosphorus/5 mL** (3 mmol Phosphorus/mL) and 22 mEq Potassium /5 mL (4.4 mEq potassium/mL) 2. **45 mmol Phosphorus/15 mL** (3 mmol Phosphorus/mL) and 66 mEq Potassium /15 mL (4.4 mEq Potassium/mL) 3. **150 mmol Phosphorus/50 mL** (3 mmol Phosphorus/mL) and 220 mEq Potassium /50 mL (4.4 mEq Potassium/mL)
Route of Administration	Injection
Rx/OTC Dispensed	Rx
Applicant	Fresenius Kabi, USA, LLC; Lake Zurich, IL
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	May 29, 2019	OPQ
Amendment, Labeling	July 11, 2019	ONDP
Amendment, Labeling	July 18, 2019	ONDP
Amendment	Aug 8, 2019	ONDP, DMA
Amendment	Aug 21, 2019	ONDP
Amendment	Sep 10, 2019	ONDP
Amendment	Sep 12, 2019	ONDP
Amendment	Oct 7, 2019	OPF
Amendment	Oct 9, 2019	ONDP
Amendment	Oct 16, 2019	OPF
Amendment	Oct 24, 2019	ONDP

Quality Review Team

DISCIPLINE	REVIEWER	Secondary Assessment
Drug Substance	Jeffrey B. Medwid	Donna Christner
Drug Product, Labeling and Environmental Assessment	Hailin (Sheena) Wang	Moo-Jhong Rhee
Process and Facilities	Peter Krommenhoek	Erin Kim
Microbiology	Denise Miller	Bryan S. Riley
Biopharmaceutics	Vincent Li	Tapash Ghosh
Regulatory Business Process Manager	Oumou Barry	N/A

Application Technical Lead	Hitesh Shroff	N/A

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Active	Reviewed by Dr. Srinivasa Murphy on January 14, 2017	LOA: Nov 5, 2018
	Type II			Active	Reviewed by Dr. Jeffrey B. Medwid on July 17, 2019	LOA: Nov 5, 2018
	Type V			Active	Last reviewed by DMA: (b) (4) on Feb 20, 2019 and (b) (4) info on Feb 6, Mar 18 and July 22, 2019	LOA Aug 15, 2018
	Type III			Active	Not reviewed, Information provided in NDA	LOA Apr 24, 2018
	Type III			Active	Not reviewed, Information provided in NDA	LOA May 5, 2018
	Type III			Active	Not reviewed, Information provided in NDA	LOA Jun 19, 2018
	Type III			Active	Not reviewed, Information provided in NDA	LOA Nov 13, 2018
	Type III			Active	Last reviewed by DMA: (b) (4) (b) (4) on Mar 1 and Mar 29, 2019	LOA Nov 13, 2018

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	130166	From the same applicant and for same indications
NDA	018892	Sodium phosphates injection from Hospira as RLD for reliance on the FDA's previous findings of safety and efficacy.
NDA	020161	Potassium Chloride injection from ICU Medical Inc.; for reliance on the FDA's previous findings of safety and efficacy.

2. CONSULTS: None

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The applicant has provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed Potassium Phosphates Injection, 3 mmol Phosphorus and 4.4 mEq Potassium/mL.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The Office of Process and Facilities (OPF) has made a final overall "Approval" recommendation for the facilities involved in this application.

The label/labeling issues have ***not*** been satisfactorily resolved as of this review.

Therefore, from the OPQ perspective, this NDA is ***not*** deemed ready for approval in its present form per CFR 314.125(b)(6), until above mentioned issues are satisfactorily resolved. **(see the List of Deficiencies)**

II. Summary of Quality Assessments

A. Product Overview

Potassium Phosphates injection is a sterile, nonpyrogenic, concentrated solution containing monobasic potassium phosphate and dibasic potassium phosphate in Water for Injection, USP, as an additive to parenteral nutrition. There are no preservatives or anti-oxidants in this formulation.

Potassium Phosphates Injection, USP products have been marketed for many years as unapproved drugs for use as supplement to intravenous solutions for parenteral nutrition.

Proposed Indication(s) including Intended Patient Population	Potassium Phosphates Injection is a phosphorus replacement product indicated as a source of phosphorus: • in intravenous fluids to correct hypophosphatemia in adults and pediatric patients when oral or enteral replacement is not possible, insufficient or contraindicated. • for parenteral nutrition in adults and pediatric patients when oral or enteral nutrition is not possible, insufficient or contraindicated.
Duration of Treatment	As needed

Maximum Daily Dose	Recommended Dosage: • Potassium Phosphates Injection provides 3 mmol/mL of phosphorus. • The dosage and rate of administration are dependent upon the individual needs of the patient. Monitor serum phosphorus, potassium and calcium and adjust the dosage accordingly. The maximum dosage is 40 millimoles of phosphate per 24 hours.
Alternative Methods of Administration	N/A

Patient Population	Generally Recommended Phosphorus Daily Dosage (Potassium Content)
Preterm and Term Infants Less than 12 Months	2 mmol/kg/day (potassium 2.9 mEq/kg/day)
Pediatric Patients 1 year to Less Than 12 years	1 mmol/kg/day; up to 40 mmol/day (potassium 1.5 mEq/kg/day; up to 58.7 mEq/day)
Adults and Pediatric Patients 12 Years of Age and Older	20 mmol/day to 40 mmol/day[a] (potassium 29.3 mEq/day to 58.7 mEq/day)

[a] In patients with moderate renal impairment (eGFR ≥30 mL/min/1.73 m² to <60 mL/min/1.73 m²), start at the low end of the dosage range.

B. Quality Assessment Overview

Drug Substances:

The active ingredients in the drug product are monobasic potassium phosphate, NF and dibasic potassium phosphate, USP.

Monobasic Potassium Phosphate, NF is a white, granular or crystalline powder. It is freely soluble in water and practically insoluble in alcohol. Its melting point is 252.6°C (decompose). Its molecular formula is KH_2PO_4 and its molecular weight is 136.09.

Manufacturing: It is manufactured by (b) (4) The complete CMC information regarding raw materials, manufacturing, purification, characterization, stability, storage and container closure is provided in DMF (b) (4). A Letter of Authorization was also submitted by the manufacturer.

The overall quality of monobasic potassium phosphate is controlled by its specification, which includes description, identification tests per USP <191> for potassium and phosphates; assay, (b) (4); bacterial endotoxins and microbial bioburden. The biopharmaceutical classification (BCS), particle size and polymorphism of monobasic potassium phosphate are not important because the drug product is an injection for intravenous administration. The applicant provided batch analyses of two batches of monobasic potassium phosphate used in the drug product manufacture.

The proposed re-test period of (b) (4) months deemed acceptable. The DMF (b) (4) was reviewed by Dr. Jeffrey B. Medwid and was deemed adequate from the CMC perspective. (See **the Drug Substance** review)

The API, potassium phosphate monobasic, manufactured by (b) (4) is controlled to conform to the requirements (specification) to produce Potassium Phosphates Injection.

Dibasic Potassium Phosphate, USP is a colorless or white, granular powder. It is freely soluble in water and very slightly soluble in alcohol. Its melting point is >465°C (decompose). Its molecular formula is K_2HPO_4 and its molecular weight is 174.20.

Manufacturing: It is manufactured by [redacted] (b) (4) The complete CMC information regarding raw materials, manufacturing, purification, characterization, stability, storage and container closure is provided in DMF [redacted] (b) (4). A Letter of Authorization is also submitted by the manufacturer.

The overall quality of dibasic potassium phosphate is controlled by its specification, which includes description, identification tests per USP <191> for potassium and phosphates; [redacted] (b) (4); bacterial endotoxins and microbial bioburden. The biopharmaceutical classification (BCS), particle size and polymorphism of dibasic potassium phosphate are not important because the drug product is an injection for intravenous administration. The applicant provided batch analyses of three batches of dibasic potassium phosphate used in the drug product manufacture.

A re-test period of [redacted] (b) (4) months is proposed by the drug product manufacturer and is deemed acceptable. The DMF [redacted] (b) (4) was reviewed by Dr. Jeffrey B. Medwid and was deemed adequate from the CMC perspective. (See **the Drug Substance** review)

The API, dibasic potassium phosphate, manufactured by [redacted] (b) (4) is controlled to conform to the requirements (specification) to produce Potassium Phosphates Injection.

Drug Product:
Potassium Phosphate Injection, USP, 3 mmol Phosphorus and 4.4 mEq Potassium/mL is a sterile, nonpyrogenic, aqueous solution of monobasic potassium phosphate and dibasic potassium phosphate. Each mL of the drug product contains 224 mg of monobasic potassium phosphate, 236 mg dibasic potassium phosphate in Water for Injection, USP. The drug product is not for direct intravenous infusion, it must be diluted or added to TPN solution prior to intravenous administration. As there are no preservatives or anti-oxidants in the drug product formulation, it is a single-use drug product and the unused portion should be discarded.

The drug product is supplied as a 5 mL, 15 mL and 50 mL plastic vial, closed with a grey rubber stopper and sealed with a flip-off cap. The 50 mL drug product is a pharmacy bulk package.

The drug product specification includes description and confirmation of potassium and phosphate per USP <191> as identity tests, assays for monobasic potassium phosphate and dibasic potassium phosphate by validated HPLC methods as tests for strength, pH, particulate matter per USP <788>, container content USP <1>, container closure integrity test and aluminum content as tests for quality and sterility per USP <71> and bacterial endotoxin per USP <85> as tests for purity. The elemental impurities were controlled per USP <232> and ICH Q3D.

The applicant provided adequate justification for the differences in the physicochemical properties between the proposed and the listed drug. Based on the information provided in accordance with 21 CFR 320.24 (b)(6) supporting the relative bioavailability of the proposed drug product to the listed drug deemed to be adequate to establish a biobridge to the agency's finding of safety and efficacy of the listed drug. Thus, an additional *in-vivo* bioequivalence (BE) bridging study is not needed. (see the **Biopharmaceutics** review).

The Potassium Phosphate Injection admixture compatibility study was conducted with 0.9% Sodium Chloride Injection and 5% Dextrose Injection (D5W) as diluents. In the compatibility study with these two diluents appearance, pH and particulate matter and stability were assessed. The admixtures were stable up to 48 hours at 25°C and up to 14 days at 5°C.

The potassium phosphate injection admixture compatibility study with TPN solutions, e.g., Clinimix-E from Baxter and Kabiven from Fresenius Kabi was performed. During the in-use stability testing no precipitates of phosphate salts were observed in the admixtures and particulate matter was within specification limits. Thus, the drug product appears to be compatible with TPN solutions, but the applicant has committed to submitting assay results of the admixture to confirm that strength is not compromised before its administration (see the PMC below).

The drug product stability testing of the drug product batches was performed in accordance with ICH Q3A(R2). Based on the satisfactory 12-month long-term stability in upright and inverted positions at 5°C and 6-month accelerated stability data at 25°C from three primary registration batches of each size of the drug product, the proposed **24-month of expiration dating period** is granted when stored at (b) (4)°C in the proposed container closure system. (see the **Drug Product** review).

Manufacturing:
Potassium Phosphates Injection, USP is manufactured by Fresenius Kabi, USA, LLC.; Grand Island, NY. The key drug product manufacturing process includes: (b) (4)

The approximate drug product batch size is (b) (4) for exhibition batches and (b) (4) for proposed commercial batches. The drug product manufacturing process, in-process controls, drug product release tests and executed batch records were reviewed and deemed satisfactory. (See **Manufacturing Integrated Assessment**)

(b) (4)

as well as the microbiology related attributes of the drug product specification including bacterial endotoxins, sterility and container closure

integrity etc. were reviewed. This NDA is recommended for approval based on drug product sterility assurance from the microbiological perspective. (See the **Microbiology** review)

Facilities:
The Office of Process and Facilities (OPF) has made an "Adequate" recommendation for all drug substance and drug product manufacturing and testing facilities. (See the **Manufacturing Integrated Assessment** review)

Environmental Assessment: Pursuant to 21 CFR § 25.31(a), Fresenius Kabi USA, LLC. (FK USA) claimed a categorical exclusion from the requirements of an environmental impact analysis statement. Under 21 CFR § 25.31(a), a categorical exclusion exists for Action on an NDA if the action does not increase the use of the active moiety.

Pursuant to 21 CFR § 25.15 (d), Fresenius Kabi USA, LLC stated that based on the best of their knowledge, no extraordinary circumstances exists that would significantly affect the quality of the human environment and would warrant the preparation of an Environmental Assessment for Monobasic Potassium Phosphate, NF and Dibasic Potassium Phosphate, USP under 21 CFR §25.21.Therefore, claim of a categorical exclusion from the requirements of an environmental assessment (EA) in accordance with 21 CFR Part 25.31(a) and 21 CFR Part 25.15 (d), was deemed acceptable. (See the **Drug Product** review)

Labeling: As of this review, the labels and labeling issues are ***not*** satisfactorily resolved from the CMC perspective according to the labeling/label review. (See the **List of Deficiencies** below and **Labeling** review).

C. Post Approval Commitment:
Submit the assay results of the TPN admixture studies as proposed in the TPN Admixture Compatibility Stability Protocol (submitted in amendment 0007 dated 09/10/2019) by December 31, 2019

D. Lifecycle Management Considerations: None
E. Special Product Quality Labeling Recommendations: None
F. Final Risk Assessment (see Attachment)

G. List of Deficiencies:
The following labeling deficiencies should be resolved with the applicant:

A. Regarding Prescribing Information

1. Revise the strength expression in the "HIGHLIGHS OF PRESCRIBING INFORMATION" and "DOSAGE FORMS AND STRENGTH" sections to the following:
   - phosphorus 15 mmol/5 mL (3 mmol/mL) and potassium 22 mEq/5 mL (4.4 mEq/mL) in a single-dose vial. (3)

- phosphorus 45 mmol/15 mL (3 mmol/mL) and potassium 66 mEq/15 mL (4.4 mEq/mL) in a single-dose vial. (3)
- phosphorus 150 mmol/50 mL (3 mmol/mL) and potassium 220 mEq/50 mL (4.4 mEq/mL) as a Pharmacy Bulk Package vial.

2. Include terms to indicate that the 50 mL presentation is intended to be used as Pharmacy Bulk Package in the "HIGHLIGHS OF PRESCRIBING INFORMATION", "DOSAGE FORMS AND STRENGTH", "HOW SUPPLIED/STORAGE AND HANDLING" sections, as well as in other relevant sections throughout the entire document.

3. In "DOSAGE AND ADMINISTRATION' section, provide preparation instructions for mixing with parenteral nutrition, and include a statement for the storage and stability of the in-use admixture for both admixture preparations.

4. Revise the description statement in Section 3: DOSAGE FORMS AND STRENGTHS statement to be the following:
"Potassium Phosphates Injection, USP is a clear and colorless solution supplied as:"

5. In the "Description" section (#11):
   - Add in the strength equivalency statement as follows:
   "Each mL contains 224 mg of monobasic potassium phosphate and 236 mg of dibasic potassium phosphate.
   Each mL contains 3 mmol phosphorus (equivalent to 93 mg phosphorous) and 4.4 mEq potassium (equivalent to 170 mg of potassium). Note: 1 mmol of phosphorus is equal to 1 mmol phosphate".
   - Revise the pharmacological class of the proposed product to "a phosphorus replacement product"
   - Include chemical name, formula and molecular weight of both active ingredients

6. In the "How supplied/storage and Handling "section (#16):
   - Revise the strength expression to the following:
   "Phosphorus 15 mmol/5 mL and Potassium 22 mEq/5 mL;
   Phosphorus 45 mmol/15 mL and Potassium 66 mEq/15 mL;
   Phosphorus 150 mmol/50 mL and Potassium 220 mEq/50 mL"
   - Revise the available units to "Tray containing 25 units"
   - Add identification of the dosage form:
   "a clear and colorless solution"
   - Add the admixture storage statement:
   "For storage of admixed solution see Dosage and Administration 2.2, 2.4".

B. Regarding Container and Carton Labels

1. Revise the strength expression on the container and tray label to the following:

(b) (4)

[redacted]

2. Include appropriate package type terms for the 50 mL presentation

Application Technical Lead Name and Date:

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
October 25, 2019

Hitesh N. Shroff -S

Digitally signed by Hitesh N. Shroff -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000348333, cn=Hitesh N. Shroff -S
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CHAPTER VI: BIOPHARMACEUTICS

Product Information	Potassium Phosphates Injection, USP
NDA Number	212832
Assessment Cycle Number	1
Drug Product Name/ Strength	Potassium Phosphates Injection, USP/ 15 mmol Phosphate and 22 mEq Potassium per 5 mL; 45 mmol Phosphate and 66 mEq Potassium per 15 mL, 150 mmol Phosphate and 220 mEq Potassium per 50 mL
Route of Administration	Intravenous
Applicant Name	Fresenius-kabi
Therapeutic Classification/ OND Division	OND/ODEIII/DGIEP
RLD/RS Number	NDA 018892 & NDA 020161
Proposed Indication	• Potassium Phosphates Injection, USP is indicated as a source of phosphorus, for addition to large volume intravenous fluids, to prevent or correct hypophosphatemia in patients with restricted or no oral intake. • It is also useful as an additive for preparing specific parenteral fluid formulas when the needs of the patient cannot be met by standard electrolyte or nutrient solutions.

Assessment Recommendation: **Adequate**

Assessment Summary:

- The focus of the biopharmaceutics review was the assessment of adequate bridging of the proposed drug product to the listed drug products.

Product Information

Potassium Phosphates Injection (3 mmol Phosphate/mL and 4.4 mEq Potassium/mL) contains the Potassium Phosphate Dibasic and Potassium Phosphate Monobasic at 18.0% w/w (236 mg/mL) and 17.1% w/w (224 mg/mL) respectively.

The proposed product is a single use sterile product hence there is no bacteriostatic agent or other preservative. There are no inactive ingredients in the proposed product. It is supplied in three fill sizes (5, 15, and 50 mL) single dose vial.

The concentrated solution is administered by intravenous route only after dilution into large volume intravenous fluids. Infusion doses of Potassium Phosphates Injection are typically prepared in 100 to 250 mL of Normal Saline (0.9% Sodium Chloride Injection USP) or D5W (5% Dextrose Injection USP) prior to administration.

The current proposed formulation is a potassium salt while the listed drug, LD [NDA 018892], for the phosphate is a sodium salt; in addition, ratio of the monobasic and dibasic is not at the same ratio/concentration as the approved (NDA 018892) reference listed drug (LD) Sodium Phosphates Injection, USP 45 mM (3 mM P/mL). However, the total Phosphate composition is 45 mM/15 mL (3 mM P/mL) which is same as the reference listed drug based on the calculation provided below.

Sodium phosphates in NDA 18892: P (mM/mL) = 142 (mg/mL of Na2HPO4)/141.96 (MW) + 276 (mg/mL of NaH2PO4.H2O)/137.99(MW) =3

Potassium Phosphates in NDA 212832: P (mM/mL) = 236 (mg/mL of KH2PO4)/136 (MW) + 224 (mg/mL K2HPO4)/174.2 (MW) = 3

The following table provides a comparison of the proposed product (potassium phosphate) and the reference product (sodium phosphate):

Parameter	Potassium Phosphates Injection	Sodium Phosphates Injection (Hospira)
Formulation	236 mg/mL of potassium phosphate dibasic, anhydrous and 224 mg/mL of potassium phosphate monobasic, monohydrate	142 mg/mL of sodium phosphate dibasic, anhydrous and 276 mg/mL of sodium phosphate monobasic, monohydrate
millimoles of Phosphorous per mL	3	3
mEq of Cation per mL	4.4 (K^+)	4 (Na^+)
Osmolarity (mOsmol/mL)	7.4	7
pH	6.7 (6.0 – 7.0)	5.5 (5.0 – 6.0)
Buffer	None	None

- The millimoles of phosphates (active moiety) is same between the proposed product and the listed drug product formulations. Any difference in the physicochemical properties of the proposed product to the reference product will not have any clinical significance as the proposed product must be diluted prior to

administration by large volume IV infusion, which dictates the final physicochemical properties of the admixture.

- The maximum daily dose of potassium is comparable to the approved products. See QT-IRT consult on 8/8/2019 in DARRT and the information below. Moreover, the safety of the potassium ion will be ensured by infusion rate of phosphate in the label.

Bridging

The Applicant proposed to rely on the Agency's previous finding of safety and efficacy of the listed drug Sodium Phosphates Injection (NDA 18892) and Potassium Chloride Injection (NDA 020161) as well as published literature and data generated by the Applicant, to satisfy the 505(b)(2) regulatory requirements for the Potassium Phosphates Injection, USP formulation.

- The active moiety of the proposed product and the listed product is phosphate. Potassium Phosphates Injection, USP provides the same phosphorus concentration (3 mmol phosphorus/mL) and will be administered at the same dosage level, for the same duration, and for the same indication as the listed drug Sodium Phosphates Injection. Because both products are in aqueous solutions, and are injected intravenously, the bioequivalence is self-evident between the two products. In addition, as the dosing is based on the active ingredient, phosphates in millimoles, the salt form does not affect the bioavailability. Therefore, the sponsor proposes that it is appropriate to bridge Potassium Phosphates Injection, USP, to the listed drug Sodium Phosphates Injection.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Application 212832 - Sequence 0001 - 0001 (1) 05/29/2019 ORIG-1 /Multiple Categories/Subcategories	**5/29/2019**
Application 212832 - Sequence 0004 - 0004 (4) 07/31/2019 ORIG-1 /Clinical/Response To Information Request	**7/31/2019**
Application 212832 - Sequence 0009 - 0009 (9) 09/12/2019 ORIG-1 /Clinical/Response To Information Request	**9/12/2019**

Highlight Key Issues from Last Cycle and Their Resolution:

- Missing comparative physicochemical properties of the proposed product and the listed products. Resolution: The applicant provided the requested information and the information provided is adequate.

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None

B.12 BRIDGING OF FORMULATIONS

Assessment: *Adequate*

- The active of the proposed product and the listed product is phosphate. Potassium Phosphates Injection, USP provides the same phosphorus concentration (3mmol phosphorus/mL) and will be administered at the same dosage level, for the same duration, and for the same indication as the listed drug Sodium Phosphates Injection. Because both products are in aqueous solutions, and are injected intravenously, the bioequivalence is self-evident between the two products. In addition, as the dosing is based on the active ingredient, phosphates in millimoles, the salt form does not affect the bioavailability. Therefore, the sponsor proposes that it is appropriate to bridge Potassium Phosphates Injection, USP, to the listed drug Sodium Phosphates Injection.

  The following information was provided by the applicant dated July 31, 2019 (SD #4) in the Response to Information Request by the Agency dated July 15, 2019:

Biopharm IR by the Agency # 1:

You plan to use Hospira's Sodium Phosphates Injection USP, 3 mM Phosphate/mL approved under NDA 018892 and ICU Medical Inc.'s Potassium Chloride Injection, 10 mEq/100 mL, 10 mEq/50 mL, 20 mEq/100 mL,30 mEq/100 mL, 20 mEq/50 mL and 40 mEq/100 mL under NDA 020161 as your reference listed drugs. We acknowledge you have submitted a biowavier. However, in absence of any PK study, the biowaiver should be submitted with adequate documentation including but not limited to comparative physicochemical (e.g., side-by side comparison of the formulations, pH, osmolality etc) properties with respect to your reference listed drugs and any other relevant data.

Consult the appropriate CFR (s) for that purpose.

In addition, discuss how K+ level will be maintained during administration of the proposed product.

The Applicant's response:

We commit to performing comparative physicochemical studies with the reference listed drugs (RLDs). The timeline for performing these studies and submitting the data/report is approximately 1 month (target submission date of September 6).

K+ level will be maintained during administration of the proposed product per the instructions in the package insert labeling as proposed in the response to query number 1 " (b) (4) .

The applicant provided comparative physicochemical studies with the reference listed drugs (RLDs) on **September 12, 2019** as described below:

Fresenius Kabi, USA was able to procure current lots of ICU Medical Inc.'s Potassium Chloride Injection (please note that the 30 mEq/100 mL presentation is not available per ICU Medical Inc.'s website). Hospira's Sodium Phosphates Injection, USP has been off the market for several years. We have limited data available for one lot of Hospira's Sodium Phosphates Injection, USP. The comparative physicochemical data with the reference listed drugs is provided in the following table:

	Fresenius Kabi's Potassium Phosphates Injection, USP	ICU Medical Inc.'s Potassium Chloride Injection					Hospira's Sodium Phosphate Injection, USP
		10 mEq / 100 mL	10 mEq / 50 mL	20 mEq / 100 mL	20 mEq / 50 mL	40 mEq / 100 mL	
Lot	Average exhibit batch result or bulk solution result used	93-023-JT	96-103-JT	01-006-JT	03-107-JT	87-012-JT	53-455-DIC
Expiry	24 months from date of manufacturing	March 1, 2020	June 1, 2020	July 1, 2020	September 1, 2020	March 1, 2020	May 1, 2017
Formulation	Dibasic Potassium Phosphate, USP: 236 mg/mL Monobasic Potassium Phosphate, NF: 224 mg/mL	Potassium Chloride, USP: 7.45 mg/mL	Potassium Chloride, USP: 14.9 mg/mL	Potassium Chloride, USP: 14.9 mg/mL	Potassium Chloride, USP: 29.8 mg/mL	Potassium Chloride, USP: 29.8 mg/mL	Dibasic Sodium Phosphate, anhydrous: 142 mg/mL Monobasic Sodium Phosphate, monohydrate: 276 mg/mL
pH per package insert	6.0 – 7.0	5.8 (4.0 - 8.0)	5.8 (4.0 - 8.0)	5.8 (4.0 - 8.0)	5.8 (4.0 - 8.0)	5.8 (4.0 - 8.0)	5.5 (5.0 – 6.0)
pH (result)	6.7	6.0	6.1	5.9	6.0	6.0	5.5
Osmolarity per package insert	7.4 mOsm/mL	0.2 mOsm/mL	0.4 mOsm/mL	0.4 mOsm/mL	0.8 mOsm/mL	0.8 mOsm/mL	7 mOsm/mL
Osmolality	Not Tested [1]	186	367	365	727	730	Not Tested [2]
(result)		mOsm/kg	mOsm/kg	mOsm/kg	mOsm/kg	mOsm/kg	
Color / Clarity	Colorless / Clear	Colorless / Clear	Colorless / Clear	Colorless / Clear	Colorless / Clear	Colorless / Clear	Colorless / Clear
Density	1.3122 g/mL	0.99942 g/mL	1.00316 g/mL	1.00568 g/mL	1.01469 g/mL	1.01419 g/mL	Not Tested [2]
Viscosity	3.40 cps	1.24 cps	1.20 cps	0.95 cps	1.22 cps	1.06 cps	Not Tested [2]

ICU Medical Inc.'s Potassium Chloride Injection is meant for direct dosage to the patient as it is much lower concentration than the other two products and is a provided in a ready to use bag format. Therefore, ICU Medical Inc.'s Potassium Chloride Injection has a lower Osmolality, Density and Viscosity compared to Fresenius Kabi's Potassium Phosphates Injection, USP. Hospira's Sodium Phosphates Injection, USP is similar to Fresenius Kabi's Potassium Phosphates Injection, USP as they are both very highly concentrated and are only to be administered after further dilution in a larger volume of fluid. Therefore, all solutions would have similar physicochemical properties upon administration.

Reviewer's Assessment: Adequate

Biopharm IR by the Agency # 2:

We note that you stated in your submission (Module 2.7.1, Section 2) that "maximum amount of potassium provided by Potassium Chloride Injection is 4 mEq which is almost similar to the amount of the potassium (4.4 mEq) provided by proposed Potassium Phosphates Injection, USP." Please clarify how this comparison in potassium amount is made under the context of infusion solution volume. In addition, provide comparison for the maximum infusion concentrations of potassium of your proposed product with the listed drug.

The Applicant's response:

FDA approved Hospira's Potassium chloride injection contains potassium per container as 10 mEq/100 mL, 10 mEq/50 mL, 20 mEq/100 mL, 30 mEq/100 mL, 20 mEq/50 mL and 40 mEq/100 mL. Hospira's Potassium Chloride product can be delivered intravenously at concentrations up to 400 mEq potassium over a 24-hour period (i.e. maximum amount of potassium is supplied through Hospira's Potassium chloride injection is 400 mEq).

Each mL of Fresenius Kabi's Potassium Phosphates Injection, USP (3 mmol/mL) consists of 224 mg of monobasic potassium phosphate (KH_2PO_4) and 236 mg of dibasic potassium phosphate (K_2HPO_4). This provides 285 mg of phosphate (93 mg of phosphorus; 3 mmol) and 170 mg of potassium (4.4 mEq). The dose and rate of administration are dependent upon the individual needs of the patient. Considering the fact, for an average adult (70 kg), the maximum proposed dose of Potassium Phosphates Injection, USP (1 mmol/kg) would deliver 102.9 mEq potassium as follow:

- Maximum dose of Potassium Phosphates Injection, USP = 1 mmol/kg = 70 mmol for 70 kg

- Amount of potassium in 3 mmol (1 mL) of Potassium Phosphates Injection, USP = 4.4 mEq

- 1 mmol of Phosphate = 4.4/3 = 1.47 mEq of Potassium

- For 70 kg person, amount of potassium delivered through Potassium Phosphates Injection, USP = 1.47 * 70 = 102.9 mEq

Overall, the maximum daily dose of potassium administered with Potassium Chloride exceeds the maximum daily dose of potassium administered with the Potassium Phosphate, proposed for correction of hypophosphatemia. Hence, maximum amount of potassium supplied through the Potassium Phosphate injection is safe. Therefore, the approved Potassium Chloride safety information is adequate to support the safety of intravenous potassium from Potassium Phosphates Injection, USP.

Reviewer's Assessment:

Considering the facts mentioned above and publicly available efficacy and safety data, Sodium Phosphates Injection, USP and Potassium Chloride Injection can be used to bridge the efficacy and safety of phosphate and potassium ion respectively to support submission of a 505(b)(2) NDA for Potassium Phosphates Injection, USP.

B. 13 BIOWAIVER REQUEST

Assessment: Based on the information provided, consistent with 21 CFR 320.24. (b)(6), FDA deemed the information supporting the relative bioavailability of the proposed drug product to the listed drug is adequate, and a biobridge has been established to the Agency's finding of safety and effectiveness for the listed drug. Thus, an additional in vivo bioequivalence (BE) bridging study is not needed.

Overall, the application is acceptable from Biopharmaceutics perspective.

Lifecycle Management Considerations

None

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Biopharmaceutics Assessor's Name and Date:

Vincent Li, 9/16/2019

Secondary Assessor Name and Date (and Secondary Summary, as needed):

CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	N 212-832
Assessment Cycle Number	01
Drug Product Name/ Strength	Potassium Phosphates Injection, USP 3 mmol P and 4.4 mEq K/mL in 5, 15, 50 mL/vial
Route of Administration	Intravenous
Applicant Name	Fresenius Kabi USA, LLC
Therapeutic Classification/ OND Division	OND/ODEIII/DGIEP
Manufacturing Site	Fresenius Kabi, Grand Island NY FEI # 3001833549
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary: The drug product is (b) (4) ***therefore the critical product attributes are the*** (b) (4) ***of the container closure system, integrity of the container closure system, the*** (b) (4) ***The stability program recorded a failure of the CCIT for one lot at the*** (b) (4) ***time point and the admixture study was not supportive of the*** (b) (4)

List Submissions being assessed (table):

Document(s) Assessed	Date Received
NDA -212832-Orig-1	**05/29/2019**

Highlight Key Issues from Last Cycle and Their Resolution: NA

Remarks: NA

Concise Description of Outstanding Issues: NA

Supporting Documents:
DMF 011240 (Drug Product Manufacturing Facility) Type V Fresenius Kabi Grand Islands manufacturing facility LOA dated 08/15/2018 for the entire DMF. This DMF contained information for the (b) (4) of the container by (b) (4) and the (b) (4) of the drug product.

The vial (b) (4) information in the DMF was recently reviewed by DMA ((b) (4) dated 02/20/2019). This review determined that the DMF is adequate and supports the proposed product for the (b) (4) of the vials in (b) (4)

The (b) (4) in (b) (4) information in the DMF was recently reviewed by DMA (D11240M16R01 dated 02/06/19 and D11240M17R01 dated 03/18/2019 and D11240M20R01 dated 07/22/2019). The reviews determined that the DMF was adequate and supports the (b) (4) of the proposed product in (b) (4).

DMF (b) (4)

(b) (4)

S DRUG SUBSTANCE: NA, drug substance is not sterile and a DMA review is not needed.

S DRUG PRODUCT:

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

The drug product is a clear colorless solution comprised of monobasic potassium phosphate and dibasic potassium phosphate in water for injection. There are no bacteriostatic agents or other preservatives added. The solution contains 3 mol

of Phosphate/mL and 4.4 mEq Potassium/mL. The product will have the following three configurations:

1) 5 mL fill (b) (4)
2) 15 mL fill (b) (4)
3) 50 mL fill (b) (4)

The composition of the drug product is the same for each configuration, only the fill volume is changed.

The container closures are:

Vials: all the vials are 20 mm finish plastic vials

Stoppers: 20 mm (b) (4) stoppers

Assessment: ***Adequate;*** the descriptions of the proposed product an container closures provided are acceptable.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

Container/Closure Integrity Testing (CCIT)

Wilcomat Differential Pressure (DP) test.

The Wilcomat DP procedure was fully described in the submission. Per the description, the test evaluates the integrity by measuring the differential pressure within the sample cylinder. A leaking vial demonstrates a larger DP value compared to the DP of the known integral vial (epoxy vial). The sensitivity of the test is $\geq 10^{-5}$ Pa•m^3/s which corresponds to a (b) (4) leak. The test procedure includes testing gross leak vial first, then a self-test simulating a (b) (4) (b) (4) leak followed by the test samples with a second bracketing (b) (4) leak self-test. The Wilcomat method at this facility has been previously reviewed for other products; the most recent being for (b) (4) and found to be adequate.

The method was validated for the subject product following USP <1207.1> for System suitability, detection of empty laser drilled vials, Accuracy, Repeatability, and Ruggedness. Acceptance criteria and results were provided

for each of the vial sizes and support the CCIT method for detecting non-integral units of the proposed drug product.

Green dye Immersion test (alternate to the Wilcomat test)
Limit: absorbance of the test sample is ≤ to (b) (4) or NMT (b) (4) in absorbance difference between the negative control sample and the test sample.

Assessment: *Adequate:* The Wilcomat leak test method had been reviewed in other applications for this facility and found acceptable. The Wilcomat test information is unchanged from previous reviews and is acceptable for this drug product. The Wilcomat leak test is also used in the stability testing to support the container closure system over the proposed shelf life.

Antimicrobial Effectiveness Testing: NA

Assessment: NA; product is single use and not preserved therefore AET is not required.

P.3 MANUFACTURE

P.3.1 MANUFACTURERS

Fresenius Kabi USA, LLC
3159 Staley Road
Grand Island New York

FEI: 3001833549

Assessment: *Adequate*

P.3.3 DESCRIPTION OF THE MANUFACTURING PROCESS AND PROCESS CONTROLS

(b) (4)

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Denise Miller

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Date: 9/20/2019 10:51:07AM
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Bryan Riley

Digitally signed by Bryan Riley
Date: 9/20/2019 10:57:24AM
GUID: 503450f200004f5816a1d3ae902b5e91

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

The Prescribing Information is deemed INADEQUATE as proposed until it is revised satisfactorily to meet the regulatory requirements (See the **List of Deficiencies** at the end of this review).

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

[redacted]

Item	Information Provided in the NDA	Assessor's Comments

Product Title in Highlights		
Proprietary name	Not proposed	
Established name(s)	Potassium Phosphates Injection	Adequate Per USP monograph title
Route(s) of administration	Injection	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	(b) (4)	**Inadequate** **Proposed revisions:** Injection: • phosphorus 15 mmol/5 mL (3 mmol/mL) and potassium 22 mEq/5 mL (4.4 mEq/mL) in a single-dose vial. (3) • phosphorus 45 mmol/15 mL (3 mmol/mL) and potassium 66 mEq/15 mL (4.4 mEq/mL) in a single-dose vial. (3) • phosphorus 150 mmol/50 mL (3 mmol/mL) and potassium 220 mEq/50 mL (4.4 mEq/mL) as a Pharmacy Bulk Package vial.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Single dose vial	**Inadequate for the 50 mL presentation.** The applicant needs to include terms to indicate that the 50 mL presentation is intended to be used as Pharmacy Bulk Package in the clinical setting as per clarification provided in SD 6 on 8/21/2019.

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

2 DOSAGE AND ADMINISTRATION

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Provided in section 2.1-2.3 as shown above	**Inadequate** The applicant provided admixture compatibility study that support the drug product to be admixed with NS, D5W. The applicant will be asked to provide preparation instruction for mixing with TPN for the nutritional supplement indication, and include a statement for the storage and stability of the in-use admixture for both cases.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Injection	**Adequate**
Strength(s) in metric system	(b) (4)	**Inadequate** **Revisions requested:** • phosphorus 15 mmol/5 mL (3 mmol/mL) and potassium 22 mEq/5 mL (4.4 mEq /mL) in a single-dose vial. • phosphorus 45 mmol/15 mL (3 mmol/mL) and potassium 66 mEq/15 mL (4.4 mEq/mL) in a single-dose vial. • phosphorus 150 mmol/50 mL (3 mmol/mL) and potassium 220 mEq/50 mL (4.4 mEq/mL) in Pharmacy Bulk Package vial.
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	(b) (4)	**Inadequate** Deletion of the (b) (4) in Section 3 is recommended.. As the (b) (4) will be included in the Description section, no need to include it here per the Labeling Tool

A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	(b) (4)	**Inadequate** **Proposed revision:** "…is a clear and colorless solution…"
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Single dose vial	**Inadequate** The applicant needs to include terms to indicate that the 50 mL presentation is intended to be used as Pharmacy Bulk Package in the clinical setting as per clarification provided in SD 6 on 8/21/2019.

1.2.4 Section 11 (DESCRIPTION)

(b) (4)

[redacted]

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Potassium phosphates Injection	Adequate
Dosage form(s) and route(s) of administration	Injection	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	(b) (4) [redacted]	**Inadequate** Proposed addition/revisions: "Each mL contains 224 mg of monobasic potassium phosphate and 236 mg of dibasic potassium phosphate. Each mL contains 3 mmol phosphorus (equivalent to 93 mg phosphorous) and 4.4 mEq potassium (equivalent to 170 mg of potassium). Note: 1 mmol of phosphorus is equal to 1 mmol phosphate".
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Water for Injection	Adequate
For parenteral injectable dosage forms, include the name and quantities of all	Water for Injection	Adequate Solution is hypertonic

inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.		
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Statement of being sterile (if applicable)	…is a sterile, non-pyrogenic, concentrated solution	Adequate
Pharmacological/ Therapeutic class	(b) (4)	**Inadequate** Proposed revision: "…, a phosphorus replacement product containing…"
Chemical name, structural formula, molecular weight	mono and dibasic potassium phosphates	**Inadequate** The applicant will need to spell out the full chemical name of the active ingredients and include chemical formula and molecular weight of both ingredients.
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	pH 6.0 to 7.0 The osmolar concentration is 7.4 mOsmol/mL (calc).	**Adequate** The product is hypertonic. Theoretical osmolar concentration is provided in Osmol per mL per USP monograph.

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and	N/A	N/A

developed by Drug Company X," "structurally unique molecular entity"		

1.2.5 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Potassium Phosphates Injection, USP (b) (4)

Product Code	Unit of Sale	Strength	Each
860529	(b) (4)		
860539			
860569			

(b) (4) Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Injection	**Adequate**
Strength(s) in metric system	(b) (4)	**Inadequate** **Proposed revisions:** Phosphorus 15 mmol/5 mL and Potassium 22 mEq/5 mL; Phosphorus 45 mmol/15 mL and Potassium 66 mEq/15 mL; Phosphorus 150 mmol/50 mL and Potassium 220 mEq/50 mL
Available units (e.g., bottles of 100 tablets)	(b) (4)	**Inadequate** **Proposed revision:** Tray containing 25 units
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Not provided NDC (b) (4) NDC NDC	**Inadequate** Proposed addition: "…is a clear and colorless solution"
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Single-dose, plastic vial; Single-dose, plastic vial; Single-dose, plastic vial;	**Inadequate** Proposed revision: 50 mL fill "Pharmacy Bulk Package, plastic vial.

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Not proposed	Adequate Results from thermal cycling study showed no effects on product quality after freezing.

If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].	**Inadequate** **Requested addition:** "For storage of admixed solution see *Dosage and Administration 2.2, 2.4*".
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	N/A
Include information about child-resistant packaging	N/A	N/A

1.2.6 Other Sections of Labeling

N/A

1.2.7 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured by: FRESENIUS KABI Lake Zurich, IL 60047 www.fresenius-kabi.com/us	Adequate

2.0 PATIENT LABELING

N/A

3.0 CARTON AND CONTAINER LABELING

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

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Potassium Phosphates Injection, USP	**Adequate**
Dosage strength	(b) (4)	**Inadequate** **Proposed revisions:** • Phosphorus 15 mmol /5 mL (3mmol/mL) Potassium 22 mEq/5 mL (4.4mEq/mL) • Phosphorus 45 mmol /15 mL (3mmol/mL) Potassium 66 mEq/15 mL (4.4mEq/mL) • Phosphorus 150 mmol /50 mL (3mmol/mL) Potassium 220 mEq /50 mL (4.4mEq/mL)
Route of administration	Injection	**Adequate**
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Each mL contains: monobasic potassium phosphate 224 mg; dibasic potassium phosphate 236 mg;	**Adequate**
Net contents (e.g. tablet count)	5 mL, 15 mL and 50 mL	**Adequate**
"Rx only" displayed on the principal display	Yes	**Adequate**
NDC number	Provided	**Adequate**
Lot number and expiration date	LOT/EXP	**Adequate**
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].	Consistent with PI and supported by stability data. **Adequate**
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Single-dose vial	**Inadequate** The applicant needs to include terms to indicate that the 50 mL presentation is intended to be used as Pharmacy Bulk Package

Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	For IV use only (b) (4)	Adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Bar code	Provided	

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Fresenius Kabi USA, LLC Lake Zurich, IL 60047	**Adequate**
Medication Guide (if applicable)	N/A	N/A
No text on Ferrule and Cap overseal	N/A	**N/A**
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	N/A
And others, if space is available	Contains no more than 2000 mcg/L of aluminum.	**Adequate** Consistent with the proposed stability limit.

Assessment of Carton and Container Labeling: ***{Not Adequate}***

See the deficiencies delineated below:

ITEMS FOR ADDITIONAL ASSESSMENT

Overall Assessment and Recommendation: Not Adequate

This application is not deemed ready for approval in its present form per 21 CFR314.125(b)(6) until the labeling/labels deficiencies delineated in the **List of Deficiencies** below are resolved satisfactorily.

List of Deficiencies:

A. Regarding Prescribing Information

1. Revise the strength expression in the "HIGHLIGHS OF PRESCRIBING INFORMATION" and "DOSAGE FORMS AND STRENGTH" sections to the following:
   - phosphorus 15 mmol/5 mL (3 mmol/mL) and potassium 22 mEq/5 mL (4.4 mEq/mL) in a single-dose vial. (3)
   - phosphorus 45 mmol/15 mL (3 mmol/mL) and potassium 66 mEq/15 mL (4.4 mEq/mL) in a single-dose vial. (3)
   - phosphorus 150 mmol/50 mL (3 mmol/mL) and potassium 220 mEq/50 mL (4.4 mEq/mL) as a Pharmacy Bulk Package vial.

2. Include terms to indicate that the 50 mL presentation is intended to be used as Pharmacy Bulk Package in the "HIGHLIGHS OF PRESCRIBING INFORMATION", "DOSAGE FORMS AND STRENGTH", "HOW SUPPLIED/STORAGE AND HANDLING" sections, as well as in other relevant sections throughout the entire document.

3. In "DOSAGE AND ADMINISTRATION' section, provide preparation instructions for mixing with parenteral nutrition, and include a statement for the storage and stability of the in-use admixture for both admixture preparations.

4. Revise the description statement in Section 3: DOSAGE FORMS AND STRENGTHS statement to be the following:
   "Potassium Phosphates Injection, USP is a clear and colorless solution supplied as:"

5. In the "Description" section (#11):
   a. Add in the strength equivalency statement as follows:
      "Each mL contains 224 mg of monobasic potassium phosphate and 236 mg of dibasic potassium phosphate.
      Each mL contains 3 mmol phosphorus (equivalent to 93 mg phosphorous) and 4.4 mEq potassium (equivalent to 170 mg of potassium). Note: 1 mmol of phosphorus is equal to 1 mmol phosphate".
   b. Revise the pharmacological class of the proposed product to "a phosphorus replacement product"
   c. Include chemical name, formula and molecular weight of both active ingredients

6. In the "How supplied/storage and Handling "section (#16):
   a. Revise the strength expression to the following:
      "Phosphorus 15 mmol/5 mL and Potassium 22 mEq/5 mL;
      Phosphorus 45 mmol/15 mL and Potassium 66 mEq/15 mL;
      Phosphorus 150 mmol/50 mL and Potassium 220 mEq/50 mL"

b. Revise the available units to "Tray containing 25 units"
c. Add identification of the dosage form:
"a clear and colorless solution"
d. Add the admixture storage statement:
"For storage of admixed solution see Dosage and Administration 2.2, 2.4".

B. Regarding Container and Carton Labels

1. Revise the strength expression on the container and tray label to the following:
   - Phosphorus 15 mmol /5 mL (3mmol/mL)
     Potassium 22 mEq/5 mL (4.4mEq/mL)
   - Phosphorus 45 mmol /15 mL (3mmol/mL)
     Potassium 66 mEq/15 mL (4.4mEq/mL)
   - Phosphorus 150 mmol /50 mL (3mmol/mL)
     Potassium 220 mEq /50 mL (4.4mEq/mL)

2. Include appropriate package type terms for the 50 mL presentation

Primary Labeling Assessor Name and Date: Hailin (Sheena) Wang, Ph.D. 10/25/2019

Secondary Assessor Name and Date (and Secondary Summary, as needed):

I agree with Dr. Wang's assessment on the labeling and labels and concur with her recommendation that this application is not ready for approval in its present form per 21CFR314125(b)(6) until the deficiencies delineated in the **List of Deficiencies** are satisfactorily resolved.

Moo-Jhong Rhee, Ph.D.
Chief, Branch V
DNDP II/ONDP

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment – NDA 212832

a) **Drug Product:** Potassium Phosphates Injection, USP, 3 mmol Phosphorus and 4.4 mEq Potassium/mL

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Precipitates in admixtures with TPN e.g. Kabiven and Clinimix E	Potential formation of calcium phosphate precipitates.	H to M	(b) (4)	No precipitates observed during the admixture in-use stability testing. Low	None
Particulate Matter in admixtures with diluents e.g. D5W and 0.9% Saline solution	Potential formation of calcium phosphate precipitates.	H to M		Particulate matter remained within acceptable range during the admixture in-use stability testing. Low	None
Bioburden	Manufacturing environment and processes	M		Bioburden is controlled in the drug product at release and stability. Low	None
Sterility	Sterilization	M		Sterility is controlled in drug product at release and stability. Low	None

Memorandum

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

Date: **November 25, 2019**

From: **Hitesh Shroff, Ph.D.**
Application Technical Lead, Branch V
Division of New Drug Products II
Office of New Drug Products

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: **CMC Review #1 of NDA 212832**

Subject: **Final Recommendation for NDA 212832**

At the time when the CMC Review #1 was completed on October 25, 2019 it had noted the following pending issues:

The label/labeling issues have not been completely resolved.

Because of these deficiencies, the NDA was not recommended for approval from the OPQ perspective.

The applicant submitted the revised the Prescribing Information (PI), immediate container and carton labels on November 21, 2019. The resubmitted CMC sections of the labeling/labels are acceptable. **(See the Attachment 1)**

Recommendation:
This NDA is now recommended for Approval from the OPQ perspective.

Application Technical Lead's Assessment and Signature

This NDA is recommended for Approval from quality perspective.

Hitesh Shroff, Ph.D.
Application Technical Lead,
Branch V Division of New Drug Products II
November 25, 2019

Hitesh N. Shroff -S

Digitally signed by Hitesh N. Shroff -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000348333, cn=Hitesh N. Shroff -S
Date: 2019.11.25 12:05:30 -05'00'

MEMORANDUM

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

DATE: November 25, 2019

TO: Review #1 of NDA 212832 Quality Assessment - Labeling

FROM: Hailin (Sheena) Wang, Ph.D.
Chemist, ONDP/DNDP II/OPQ

THROUGH Moo-Jhong Rhee, Ph.D.
Chief, Branch V
DNDP II/ONDP/OPQ

SUBJECT: **Final Recommendation on Labeling/Labels**

SUMMARY

The previous Quality Labeling Review #1 dated 10/25/2019, made a recommendation of not ready for approval of this NDA because of labeling deficiencies (see N212832 IQA Labeling R1). These labeling issues have been satisfactorily resolved based on the revisions made in SD 16, SD 18 and SD19.

RECOMMENDATION:
This application is now recommended for **Approval** from the Quality labeling/label perspective.

Assessment Notes

FDA labeling request along with additional labeling comments were communicated to the applicant on 10/25/2019. Subsequently, the following amendments were submitted and assessed.

List Submissions being reviewed:

Document Reviewed (eCTD #)	Date Received
eCTD-0016 (SD-16)	10/30/2019
eCTD-0017 (SD-17)	11/12/2019
eCTD-0018 (SD-18)	11/18/2019
eCTD-0019 (SD-19)	11/21/2019

Review of the applicant's IR response is provided below:

List of recommended revisions sent to the applicant on 10/25/2019:

A. Regarding Prescribing Information

1. Revise the strength expression in the "HIGHLIGHS OF PRESCRIBING INFORMATION" and "DOSAGE FORMS AND STRENGTH" sections to the following:
   - phosphorus 15 mmol/5 mL (3 mmol/mL) and potassium 22 mEq/5 mL (4.4 mEq/mL) in a single-dose vial. (3)
   - phosphorus 45 mmol/15 mL (3 mmol/mL) and potassium 66 mEq/15 mL (4.4 mEq/mL) in a single-dose vial. (3)
   - phosphorus 150 mmol/50 mL (3 mmol/mL) and potassium 220 mEq/50 mL (4.4 mEq/mL) as a Pharmacy Bulk Package vial.

2. Include terms to indicate that the 50 mL presentation is intended to be used as Pharmacy Bulk Package in the "HIGHLIGHS OF PRESCRIBING INFORMATION", "DOSAGE FORMS AND STRENGTH", "HOW SUPPLIED/STORAGE AND HANDLING" sections, as well as in other relevant sections throughout the entire document.

3. In "DOSAGE AND ADMINISTRATION' section, provide preparation instructions for mixing with parenteral nutrition, and include a statement for the storage and stability of the in-use admixture for both admixture preparations.

4. Revise the description statement in Section 3: DOSAGE FORMS AND STRENGTHS statement to be the following:
   "Potassium Phosphates Injection, USP is a clear and colorless solution supplied as:"

5. In the "Description" section (#11):
   a. Add in the strength equivalency statement as follows:

"Each mL contains 224 mg of monobasic potassium phosphate and 236 mg of dibasic potassium phosphate.
Each mL contains 3 mmol phosphorus (equivalent to 93 mg phosphorous) and 4.4 mEq potassium (equivalent to 170 mg of potassium). Note: 1 mmol of phosphorus is equal to 1 mmol phosphate".

b. Revise the pharmacological class of the proposed product to "a phosphorus replacement product"
c. Include chemical name, formula and molecular weight of both active ingredients

6. In the "How supplied/storage and Handling "section (#16):
   a. Revise the strength expression to the following:
   "Phosphorus 15 mmol/5 mL and Potassium 22 mEq/5 mL;
   Phosphorus 45 mmol/15 mL and Potassium 66 mEq/15 mL;
   Phosphorus 150 mmol/50 mL and Potassium 220 mEq/50 mL"
   b. Revise the available units to "Tray containing 25 units"
   c. Add identification of the dosage form:
   "a clear and colorless solution"
   d. Add the admixture storage statement:
   "For storage of admixed solution see Dosage and Administration 2.2, 2.4".

Applicant response in SD 16 on 10/30/2019:
Our proposed draft labeling has been revised to address all the Agency's comments/suggestions.

Related information/revisions provided in SD 16 and SD19:

HIGHLIGHTS OF PRESCRIBING INFORMATION

---------- **DOSAGE FORMS AND STRENGTHS** ----------
Injection:
- phosphorus 15 mmol/5 mL (3 mmol/mL) and potassium 22 mEq/5 mL (4.4 mEq/mL) in a single-dose vial. (3)
- phosphorus 45 mmol/15 mL (3 mmol/mL) and potassium 66 mEq/15 mL (4.4 mEq/mL) in a single-dose vial. (3)
- phosphorus 150 mmol/50 mL (3 mmol/mL) and potassium 220 mEq/50 mL (4.4 mEq/mL) as a Pharmacy Bulk Package vial.

SECTION 2 (DOSAGE AND ADMINISTRATION)

2.1 Preparation and Administration in Intravenous Fluids to Correct Hypophosphatemia

…

Storage and Stability

- *Single-Dose Vial (5 mL and 15 mL)*
  - For single use only. Discard used vial, including any unused contents.
- *Pharmacy Bulk Package Vial (50 mL)*
  - Penetrate vial closure only one time with a suitable sterile transfer device or dispensing set that allows measured dispensing of the contents.
  - Use Potassium Phosphates Injection promptly once the sterile transfer set has been inserted into the Pharmacy Bulk Package vial

or a maximum of 4 hours at room temperature 20°C to 25°C (68°F to 77°F) (25ºC to 77ºF) after the container closure has been penetrated. Discard any remaining drug.

2.3 Preparation and Administration in Parenteral Nutrition

- Potassium Phosphates Injection is for *intravenous infusion* into a peripheral or central vein *only after dilution and admixing*.

- Potassium Phosphates Injection is to be prepared only in a suitable work area such as a laminar flow hood (or an equivalent clean air compounding area). The key factor in the preparation is careful aseptic technique to avoid inadvertent touch contamination during mixing of solutions and addition of other nutrients.

- Transfer the required amount of Potassium Phosphates Injection to the parenteral nutrition solution following the admixture of amino acids, dextrose, electrolytes solutions, and prior to lipids (if added).

- Because additives may be incompatible, evaluate all additions to the parenteral nutrition container for compatibility and stability of the resulting preparation.

- Calcium and phosphate ratios must be considered. Excess addition of calcium and phosphate, especially in the form of mineral salts, may result in the formation of calcium-phosphate precipitates *[see Warnings and Precautions (5.2)]*. Calcium-phosphate stability in parenteral nutrition solutions is dependent upon the pH of the solution, temperature, and relative concentration of each ion. Discard if any precipitates are observed.

- Inspect the final parenteral solution containing Potassium Phosphates Injection to ensure that:
  - precipitates have not formed during mixing or addition of additives and inspect again before administration.
  - the emulsion has not separated, if lipids have been added. Separation of the emulsion can be visibly identified by a yellowish streaking or the accumulation of yellowish droplets in the admixed emulsion.

- The final parenteral nutrition solution is for intravenous infusion into a peripheral or central vein. The choice of a peripheral or central venous route should depend on the osmolarity of the final infusate. Solutions

with osmolarity of 900 mOsm/L or greater must be infused through a central catheter *[see Warnings and Precautions (5.7)]*.

Storage

- Protect the parenteral nutrition solution from light during storage.

Stability

- *Single-Dose Vial (5 mL and 15 mL)*
  - For single use only. Discard used vial, including any unused contents.
- *Pharmacy Bulk Package Vial (50 mL)*
  - Penetrate vial closure only one time with a suitable sterile transfer device or dispensing set that allows measured dispensing of the contents.
  - Use Potassium Phosphates Injection for admixing promptly once the sterile transfer set has been inserted into the Pharmacy Bulk Package vial or a maximum of 4 hours at room temperature 20°C to 25°C (68°F to 77°F) (25ºC to 77ºF) after the container closure has been penetrated. Discard any remaining drug.
- Use parenteral nutrition solutions containing Potassium Phosphates Injection promptly after mixing. Any storage of the admixture should be under refrigeration from 2°C to 8°C (36°F to 46°F) and limited to a brief period of time, no longer than 24 hours. After removal from refrigeration, bring to room temperature and use promptly and complete the infusion within 24 hours. Discard any remaining admixture.

SECTION 3 (DOSAGE FORMS AND STRENGTHS)

Potassium Phosphates Injection, USP is a clear and colorless solution supplied as:

- phosphorus 15 mmol/5 mL (3 mmol/mL) and potassium 22 mEq/5 mL (4.4 mEq /mL) in a single-dose vial.
- phosphorus 45 mmol/15 mL (3 mmol/mL) and potassium 66 mEq/15 mL (4.4 mEq/mL) in a single-dose vial.
- phosphorus 150 mmol/50 mL (3 mmol/mL) and potassium 220 mEq/50 mL (4.4 mEq/mL) in Pharmacy Bulk Package vial.

SECTION 11 (DESCRIPTION)

Potassium Phosphates Injection, USP, a phosphorus replacement product containing phosphorus 3 mmol/mL and potassium 4.4 mEq/mL. It is a sterile, non-pyrogenic,

concentrated solution containing a mixture of monobasic potassium phosphate and dibasic potassium phosphate in water for injection. It is supplied as a 5 mL and 15 mL single-dose vials and a 50 mL Pharmacy Bulk Package vial.

Monobasic Potassium Phosphate is chemically designated KH_2PO_4, molecular weight 136.09, white, odorless crystals or granules freely soluble in water.

Dibasic Potassium Phosphate is chemically designated K_2HPO_4, molecular weight 174.18, colorless or white granular salt freely soluble in water.

Each mL contains 224 mg of monobasic potassium phosphate and 236 mg of dibasic potassium phosphate.

Each mL contains 3 mmol phosphorus (equivalent to 93 mg phosphorus) and 4.4 mEq potassium (equivalent to 170 mg of potassium). Note: 1 mmol of phosphorus is equal to 1 mmol phosphate. The pH is 6.0 to 7.0.

This product contains no more than 2000 mcg/L of aluminum [see Warnings and Precautions (5.5)].

The osmolar concentration is 7.4 mOsmol/mL (calc).

The solution is administered after dilution or admixing by the intravenous route.

SECTION 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Potassium Phosphates Injection, USP is a clear and colorless solution supplied as phosphorus 3 mmol/mL and potassium 4.4 mEq/mL as shown:

Product Code	Unit of Sale	Strength	Each
860529	NDC 65219-052-29 Tray containing 25 units	Phosphorus 15 mmol/5 mL and Potassium 22 mEq/5 mL	NDC 65219-052-09 5 mL single dose, plastic vial
860539	NDC 65219-054-29 Tray containing 25 units	Phosphorus 45 mmol/15 mL and Potassium 66 mEq/15 mL	NDC 65219-054-09 15 mL single dose, plastic vial
860569	NDC 65219-056-29 Tray containing 25 units	Phosphorus 150 mmol/50 mL and Potassium 220 mEq/50 mL	NDC 65219-056-09 50 mL fill Pharmacy Bulk Package, plastic vial.

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Pharmacy Bulk Package vial: Discard within 4 hours of initial entry *[see Dosage and Administration (2.3)]*.

For storage of admixed solution *see Dosage and Administration 2.1, 2.3.*

Reviewer's Assessment: Adequate

The applicant accepted the strength expression per FDA's recommendation throughout the labeling document.

The applicant accepted the added package type terms to indicate that the 50 mL presentation is intended to be used as Pharmacy Bulk Package in all relevant sections throughout the entire labeling document.

The applicant agreed to include preparation instructions for mixing with parenteral nutrition, and a statement for the storage and stability of the in-use admixture for both admixture preparations.

The pharmacological class, strength equivalency statement, and chemical name, formula and molecular weight of both active ingredients have been added per FDA's recommendation.

Lastly, the identification of the dosage form and admixture storage statement have been added per FDA's recommendation.

List of recommended revisions sent to the applicant on 10/25/2019:

B. Regarding Container and Carton Labels

1. Revise the strength expression on the container and tray label to the following:
   - Phosphorus 15 mmol /5 mL (3mmol/mL)
     Potassium 22 mEq/5 mL (4.4mEq/mL)
   - Phosphorus 45 mmol /15 mL (3mmol/mL)
     Potassium 66 mEq/15 mL (4.4mEq/mL)
   - Phosphorus 150 mmol /50 mL (3mmol/mL)
     Potassium 220 mEq /50 mL (4.4mEq/mL)

2. Include appropriate package type terms for the 50 mL presentation [redacted] (b) (4)

List of recommended revisions sent to the applicant via email on 11/15/2019:
Please add the following to the respective labeling:
Carton and Container Labels (Pharmacy Bulk Package):
• Discard within 4 hours of initial entry

Section 16 of the PI:
• Pharmacy Bulk Package vial: Discard within 4 hours of initial entry [see Dosage and Administration (2.3)].

List of recommended revisions sent to the applicant via email on 11/20/2019:

Please revise the statement below for all presentations of the Carton and Container Labels:
• Each mL provides: 3 mmol phosphorus and 4.4 mEq of potassium

Most recent draft labels provided in SD 19 on 11/25/2019

CONTAINER LABEL

(b) (4)

Reviewer's Assessment: Adequate

As shown above, the applicant has revised the strength expression on the container & tray labels and added the package type term for the 50mL presentation.

In addition, the applicant changed (b) (4) to "phosphorus" in the equivalency statement for all container and tray labels. Although microbial growth is considered low risk for the concentrated product which is hyperosmotic, a statement about discarding after 4 hours on the PBP vial was added per FDA's request as a precaution.

Sheena Hailin Wang

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Moo Jhong Rhee

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Hitesh Shroff

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