CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212832Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 19, 2019
Requesting Office or Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Application Type and Number:	NDA 212832
Product Name and Strength:	Potassium Phosphates Injection, USP
Total Product Strength:	Phosphorus 15 mmol/5 mL (3 mmol/mL) and Potassium 22 mEq/5 mL (4.4 mEq/mL) Phosphorus 45 mmol/15 mL (3 mmol/mL) and Potassium 66 mEq/15 mL (4.4 mEq/mL) Phosphorus 150 mmol/50 mL (3 mmol/mL) and Potassium 220 mEq/50 mL (4.4 mEq/mL) Phosphorus 15 mmol and Potassium 22 mEq per 5 mL Phosphorus 45 mmol and Potassium 66 mEq per 15 mL Phosphorus 150 mmol and Potassium 220 mEq per 50 mL
Applicant/Sponsor Name:	Fresenius Kabi USA, LLC
OSE RCM #:	2019-1135-2
DMEPA Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Idalia E. Rychlik, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on November 18, 2019 for Potassium Phosphates Injection, USP. Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that we review the revised container labels and carton labeling for Potassium Phosphates Injection, USP (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

[a] Abraham, S. Label and Labeling Review for Potassium Phosphates Injection, USP (NDA 212832). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 13. RCM No.: 2019-1135-1

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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

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

Memorandum

Date: November 14, 2019

To: Thao Vu, Regulatory Project Manager, (DGIEP)

Joette Meyer, Associate Director for Labeling, (DGIEP)

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Team Leader, OPDP

Subject: OPDP Labeling Comments for POTASSIUM PHOSPHATES injection, for intravenous use

NDA: 212832

In response to DGIEP's consult request dated May 31, 2019, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for potassium phosphates.

PI: OPDP has no comments on the proposed labeling are based on the draft PI retrieved from SharePoint on November 14, 2019.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the sponsor, and retrieved from SharePoint on November 14, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 13, 2019
Requesting Office or Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Application Type and Number:	NDA 212832
Product Name and Strength:	Potassium Phosphates Injection, USP
Total Product Strength:	Phosphorus 15 mmol/5 mL (3 mmol/mL) and Potassium 22 mEq/5 mL (4.4 mEq/mL) Phosphorus 45 mmol/15 mL (3 mmol/mL) and Potassium 66 mEq/15 mL (4.4 mEq/mL) Phosphorus 150 mmol/50 mL (3 mmol/mL) and Potassium 220 mEq/50 mL (4.4 mEq/mL) Phosphorus 15 mmol and Potassium 22 mEq per 5 mL Phosphorus 45 mmol and Potassium 66 mEq per 15 mL Phosphorus 150 mmol and Potassium 220 mEq per 50 mL
Applicant/Sponsor Name:	Fresenius Kabi USA, LLC
OSE RCM #:	2019-1135-1
DMEPA Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Idalia E. Rychlik, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on October 30, 2019 for Potassium Phosphates Injection, USP. Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that we review the revised container labels and carton labeling for Potassium Phosphates Injection, USP (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

[a] Abraham, S. Label and Labeling Review for Potassium Phosphates Injection, USP (NDA 212832). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 OCT 15. RCM No.: 2019-1135.

2 CONCLUSION

The revised container labels and carton labeling are unacceptable from a medication error perspective. Below, we have provided recommendations in Table 1. We ask that the Division convey Table 1 in its entirety to Fresenius Kabi USA, LLC so that recommendations are implemented prior to approval of this NDA.

3 RECOMMENDATIONS FOR FRESENIUS KABI USA, LLC

We recommend the following be implemented prior to approval of this NDA:

Table 1. Identified Issues and Recommendations for Fresenius Kabi USA, LLC (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
All Container Labels and Carton Labeling			
1.	There is inadequate differentiations between the 5 mL and 15 mL vials.	The use of the same (b) (4) color and identical format minimizes the difference between the 5 mL and 15 mL single dose vials, which may lead to wrong strength selection errors and over-dose or under-dose of patients.	Consider the use of different colors, boxing, or some other means to provide adequate differentiation between the 5 mL and 15 mL carton labeling and container labels.
2.	As proposed, the expiration date format may cause deteriorated drug product errors.	The following proposed expiration date format: MM/YY, where MM (month) numerical characters may be misunderstood for date and the YY (year) maybe confused for either the month and/or date.	Change the expiration date to the format requested below. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may

Table 1. Identified Issues and Recommendations for Fresenius Kabi USA, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
3.	As proposed, an undefined numeric [the Fresenius Kabi internal part number (XXXXXX)] will be printed on the marketed carton labeling and container labels directly above the Lot and Exp date.	The close proximity of another number near the lot number statement can be mistaken for the lot number. [b] As well as, may cause confusion with deciphering the correct expiration date.	If the Fresenius Kabi internal part number (XXXXXX) will be printed on the marketed carton labeling and container labels, define the numeric and/or consider relocating it to another part of the labels and labeling.
4.	As currently displayed, the net quantity statement is as prominent as the product strength statement and takes the reader's attention away from more important product information such as the strength.	Post-marketing experience shows that the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is more prominent.	Decrease the prominence of the net quantity statement by unbolding and/or decreasing the font size. Consider relocating it to the bottom right-hand side of the Principal Display Panel (PDP) away from the strength statement.
5.	National Drug Code (NDC) number, specifically the product code is more prominent than the strength statement.	The product name, the strength and the cautionary statements should be the most prominent information on the PDP.	Decrease the prominence of the NDC number.

[b] Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs/Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone: 301-796-2200
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PEDIATRIC LABELING REVIEW

From:	Carolyn L. Yancey, MD, Medical Officer Division of Pediatric and Maternal Health (DPMH)
Through:	Hari Cheryl Sachs, MD, Pediatric Team Leader, DPMH John J. Alexander, MD, MPH, Deputy Director, DPMH
NDA Number:	212832
Sponsor:	Fresenius Kabi USA, LLC
Drug:	Potassium Phosphates Injection
Drug Class:	Parenteral Phosphorus Replacement
Dosage Form, Strength, Route of Administration:	Injection, for intravenous (IV) use: - 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 a Pharmacy Bulk vial
Approved Indication:	None (Note, a Potassium Phosphates Injection product under NDA 212121 is approved for patients 12 years and older).
Proposed Indication:	Potassium Phosphates Injection 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 solution.
Proposed Dosing Regimen:	The dosage is dependent upon the individual needs of the patient, and the contribution of phosphorus and potassium from other sources. Based on clinical requirements, some patients may require a lower or higher dose. The maximum initial or single dose of phosphorus is 45 mmol (potassium 66 mEq).
Consult Request:	The Division of Gastroenterology and Inborn Errors Products (DGIEP)

requests the DPMH Pediatric Team review of pediatric labeling for the new drug application (NDA) 212832 for Potassium Phosphates Injection, 3 mmol Phosphate and 4.4 mEq Potassium/mL (5 mL, 15 mL, and 50 mL/vial, manufactured by Fresenius Kabi USA, LLC (Fresenius). NDA 212832 is submitted via a 505(b)(2) regulatory pathway relying on two listed products, Sodium Phosphates Injection, 45 mmol (3 mmol phosphate/ mL) under NDA 018892 by Hospira, Incorporated, and Potassium Chloride Injection under NDA 020161 by ICU Medical, Incorporated. DPMH will assist with pediatric labeling recommendations. The consult is due on October 25, 2019 (consult is dated June 4, 2019).

Background

There are two reference products for NDA 212832 submitted under a 505(b)(2) regulatory pathway:

- Sodium Phosphates Injection (NDA 018892 by Hospira) was FDA-approved on May 10, 1983 as 45 mM (3 mM phosphorus/mL) which also contains 4 mEq/mL sodium. Sodium phosphates is a sterile, nonpyrogenic, concentrated solution containing a mixture of monobasic sodium phosphate and dibasic sodium phosphate in water for injection provided as a 15 mL partial fill, single-dose vial.[1] Sodium Phosphates Injection is indicated for all ages, including neonates as " a source of phosphorus, for addition to large volume IV 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." [2] The solution with sodium phosphates is intended as an alternative to potassium phosphate to provide phosphorus for addition to large volume infusion fluids for intravenous use. Approved labeling for sodium phosphates includes dosing for all ages, including neonates. Sodium phosphates injection labeling includes precautions in patients with renal impairment, cirrhosis, cardiac failure and other edematous or sodium-retaining conditions.[3]

  <u>Reviewer Comments</u>: DPMH notes that labeling for Sodium Phosphates Injection does not include specific weight-based pediatric dosing for neonates through patients less than 18 years of age.

- Potassium Chloride Injection (NDA 020161 by ICU Medical Incorporated) was FDA-approved on November 30, 1992 as potassium 10 mEq/5ml[4] for single-dose infusion after dilution in a suitable large volume parenteral for treatment of potassium deficiency states when oral replacement is not feasible. Per labeling, "This highly concentrated, ready-to-use potassium chloride injection is intended for the maintenance of serum potassium levels and for potassium supplementation in fluid restricted patients who cannot accommodate additional volumes of fluid associated with potassium solutions of lower concertation".[5] Labeling for NDA 020161 Potassium Chloride does not include recommendations on dosing for pediatric patients of any age.

Of note, on September 19, 2019, FDA approved a similar potassium phosphate product, NDA 212121 Potassium Phosphates Injection by CMP Development, LLC, as a source of phosphorus indicated in intravenous fluids to correct hypophosphatemia in adults and pediatric patients 12 years of age and older

[1] NDA 018892 Sodium Phosphates Injection by Hospira (approved on May 10, 1983), see Description and Clinical Pharmacology (PLR format).
[2] NDA 018892 Sodium Phosphates Injection by Hospira, see Indications and Usage (PLR format).
[3] NDA 018892 Sodium Phosphates Injection by Hospira, see Precautions (PLR format).
[4] NDA 020161 Potassium Chloride also labeled as an additive solution (concentration and size) potassium 20 mEq/10 mL, 30 mEq/15 mL, and 40 mEq/20 mL.
[5] NDA 020161 Potassium Chloride Injection by ICU Medical, Inc. (approved November 30, 1992), see Indications and Usage (PLR format).

when oral or enteral replacement is not possible, insufficient or contraindicated and for parenteral nutrition in adults weighing at least 45 kg and pediatric patients 12 years of age and older weighing at least 40 kg when oral or enteral nutrition is not possible, insufficient or contraindicated. Labeling includes a Limitation of Use because "safety has not been established for parenteral nutrition in adults weighing less than 45 kg or pediatric patients less than 12 years of age weighing less than 40 kg due to the risk of aluminum toxicity".[6] This CMP product contains no more than 15,000 mcg/L of aluminum as described in approved labeling (dated September 19, 2019) which may exceed toxic levels when administered at the recommended dosage. Patients with renal impairment, including pre-term infants, who receive greater than 4 to 5 mcg/kg/day of parenteral aluminum, can accumulate aluminum to levels associated with central nervous system and bone toxicity. Potentially toxic levels of aluminum may occur with prolonged parenteral administration if kidney function is impaired. Preterm infants are particularly at risk for aluminum toxicity because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which also contain aluminum.[7]

For the CMP product, the dose of phosphorus and rate of administration needs to be individualized based on careful monitoring of serum potassium, phosphorus, calcium, and magnesium. Each mL contains 175 milligrams (mg) of monobasic potassium phosphate, (b) (4) and 300 mg of dibasic potassium phosphate, (b) (4). One mmol of phosphorus weighs 31 mg, and the product provides 93 mg (approximately 3 mmol) of phosphorus/mL and 4.7 mEq of potassium/mL".[8] The maximal adult and adolescent phosphorus dosage is 45 millimoles of phosphorus per 24 hours based on the potassium content.

The pre-approval review cycles of the two potassium phosphate products (NDA 212121 and NDA 212832) were partially concurrent. NDA 212121, received by FDA on March 19, 2019 and approved on September 19, 2019. Labeling under this DPMH review for NDA 212832 Potassium Phosphates Injection by Fresenius was received on May 29, 2019 and addresses two indications for adults and all pediatric patients down to neonates as well as a dosing regimen for neonates to patients less than 12 years of age. The aluminum content for Potassium Phosphates Injection under NDA 212832 by Fresenius contains no more than 2,000 mcg/L of aluminum and is therefore, acceptable in adult and pediatric patients down to neonates.

Fresenius proposes an indication for Potassium Phosphates Injection "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."[9] No clinical trials were performed by the applicant because this NDA relies on FDA findings of safety from the two listed drugs (NDA 018892 and NDA 020161) cited above as well as published literature that supports the safety of and dosing regarding the potassium salt. This DPMH labeling review addresses a new dosing regimen in pediatric patients less than 12 years down to neonates for use as a source of phosphorus replacement and for parenteral nutrition.

Reviewer Comment:
This proposed formulation has acceptable levels of aluminum for the youngest pediatric patients down to neonates (cited earlier in this review) and therefore, will be recommended in adult and pediatric patients down to neonates. The applicant's maximum proposed dose contains (b) (4) *µg aluminum total* (b) (4) *mcg /kg/day); this amount does not exceed the threshold for aluminum toxicity in pediatric patients of 4 to 5 mcg/kg/day of parenteral aluminum. Per the Pharmacology Toxicology Reviewer for this NDA, for a pediatric patient (i.e., weighing 2.5 kg) exposure to aluminum at 2000 mcg/L, based on a maximum daily dose of phosphorus 2 mmol/kg/day (5 mmol/day over 3 mmol/mL equals 1.7 mL/day) will be 1.4 mcg/kg/day.*

[6] NDA 212121 Potassium Phosphates injection by CMP approved labeling (dated September 19, 2019)
[7] See 21 Code of Federal Regulations (CFR): https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=201.323
[8] NDA 212121 Potassium Phosphates Injection by CMP proposed labeling see Section 11 Description (per DGIEP dated August 26, 2019).
[9] NDA 212832 Potassium Phosphates Injection by Fresenius Kabi USA, LLC, see Indications and Usage (dated May 2019 per the applicant)

Safety risks of aluminum toxicity (i.e. central nervous system and bone toxicity) are addressed in the proposed substantially complete labeling for Potassium Phosphates Injection [see Warnings and Precautions (5.6) and Pediatric Use (8.4)].

Pediatric Research Equity Act Requirements
Under 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. Fresenius proposes a new dosing regimen for the potassium phosphates product, specifically weight-based dosing in pediatric patients less than 12 years of age down to neonates for the indications cited earlier in this review. Therefore, PREA applies based the proposed new dosing regimen. See below for summary of the applicant's pediatric assessment based on published literature and clinical practice guidelines.

Agreed initial Pediatric Study Plan
An Agreed iPSP (dated October 19, 2018) under investigational new drug (IND) 130166 includes: plans to perform a pediatric assessment (to be submitted with the planned NDA) based upon data in published literature, clinical practice guidelines and/or published white papers to support the proposed indications (cited earlier in this review) and dosing in all ages.

Reviewer Comments: This iPSP was discussed at PeRC on October 17, 2018 and the committee concurred with the general plan for an assessment. DPMH defers to Pharmacology Toxicology and Chemistry and Manufacturing Controls (CMC) on the acceptability of the level of aluminum in this formulation proposed for administration in the youngest pediatric patients down to neonates. The planned NDA submission was projected for submission to FDA 2nd quarter 2019.

NDA 212832 Potassium Phosphates Injection Pediatric Assessment
The applicant proposes to rely on extrapolation from adult data based on extensive clinical experience with the dosing regimen for Sodium Phosphates Injection as well as Potassium Chloride Injection and supported by published literature and clinical guidelines. There are no adequate and well-controlled clinical studies in pediatric patients or pharmacokinetic (PK) studies. Phosphorus (P) is a major intracellular mineral and is particularly important in bone mineralization. In newborn infants' total body P is ~16g with ~80% in bone and 9% in skeletal muscle. In the kidney, 85-90% of the filtered phosphate is reabsorbed. In the presence of low phosphate intake, the kidney of the infant adapts by retaining P and excreting a urine devoid of P. Hypercalcemia and hypercalciuria result from P deficiency. Excessive loading of P results in hyperphosphatemia, hypokalemic tetany, and secondary hyperparathyroidism. Deficiency of P also results in decreased bone mineralization and rickets.[10]

DPMH and DGIEP have previously determined that published literature and clinical practice guidelines were sufficient to establish dosing of potassium phosphates in adolescent patients (under NDA 212121 Potassium Phosphates by CMP). Phosphorus dosing and total parenteral nutrition (TPN) requirements in younger pediatric patients, including neonates are described in clinical practice guidelines for parenteral nutrition formulation recommendations[11] as well as a single daily bolus dosing recommendation.[12,13] The applicant

[10] Greene HL et al. Guidelines for the use of vitamins, trace elements, calcium, magnesium, and phosphorus in infants and children receiving total parenteral nutrition: report of the Subcommittee on Pediatric Parenteral Nutrient Requirements from the Committee on Clinical Practice Issues of The American Society for Clinical Nutrition, Am J Clin Nur 1988; 48:1324-42
[11] The Harriett Lane Handbook, A Manual for Pediatric House Officers (2[1st] Edition), Chapter 21 Nutrition and Growth, Initiation and
[12] Advancement of Parenteral Nutrition, American Society for Parenteral and Enteral Nutrition (ASPEN). Safe practices for parenteral nutrition. JPEN 2004; 28(6):S39-S70.
[13] Lexicomp Pediatric & Neonatal Dosage Handbook – An Extensive Resource for Clinicians Treating Pediatric and Neonatal Patients. 2017

used published literature to recommend once daily dosing in pediatric patients based on laboratory reference ranges for serum phosphate and potassium. Per the Pediatric Nutrition Handbook, 5th Edition, the American Academy of Pediatrics (AAP)[14], based on ideal body weight (50th percentile for length or height), see **Table 1** for mineral supplements for parenteral nutrition for pre-term infants and **Table 2** for the components of maintenance parenteral nutrition in infants and toddlers, children, and adolescents.

Table 1. Mineral Supplements for Parenteral Nutrition for Pre-Term Infants per Kilogram

Mineral	Recommended Dosage
Calcium	80-100 mg
Phosphorus	43-62 mg
Magnesium	6-10 mg

Source: Modified from the Pediatric Nutrition Handbook, 5th Ed, AAP, Table 2.3, page 44.

Table 2. Components of Maintenance Parenteral Nutrition in Infants and Children

	Weight		
Base Components	**< 10 kg**	**10 - 20 kg**	**> 20 kg**
Fluid	100 - 150 mL/kg	1000 mL + 50 mL/kg > 10 kg	1500 mL + 20 mL/kg > 20 kg
Calories, kcal/kg* Dextrose, g/kg (3.4 kcal/g)	80 - 130 10 - 30	60 - 90 8 - 28	30 - 75 5 - 20
Protein, g/kg * (1 g protein = 0.16 g nitrogen)	1.5 - 3	1 - 2.5	0.8 - 2.0
Fat, g/kg	0.5 - 4	1 - 3	1 - 3
Additive	**Infants and Toddlers**	**Children**	**Adolescents**
Sodium	2-4 mEq/kg	2-4 mEq/kg	60-150 mEq
Potassium	2-4 mEq/kg	2-4 mEq/kg	70-180 mEq
Chloride	2-4 mEq/kg	2-4 mEq/kg	60-150 mEq
Phosphorus (31 mg/ mmol)	0.5-2 mmol.kg	0.5-2 mmol/kg	9-30 mmol/kg

Source: Modified from the Pediatric Nutrition Handbook, 5th Ed, AAP, Table 22.2, page 373.

* Ideal weight (50th percentile for length or height).

Clinical practice guidelines vary in general ranges depending on a patient's clinical condition and organ function, particularly renal status. DPMH considered the guideline variability when recommending the dose ranges for potassium phosphates injection. By example, appropriate dosing for parenteral nutrition per the ASPEN Recommendations is shown in **Table 3** for electrolytes and minerals.[15]

Table 3. Electrolyte and Minerals

Nutrient	Standard Daily Requirement	Factors that increase needs
Phosphorus*	20-40 mmol	High dextrose intake, refeeding

Source: Modified from ASPEN, American Society for Parenteral and Enteral Nutrition, January 18, 2019.

* Use caution in prescribing calcium and phosphorus related to compatibility.

Wolters Kluwer Clinical Drug Information.

[14] Pediatric Nutrition Handbook 5th Ed. By Ronald E. Kleinman, MD, Editor, Section IV Nutrient Delivery Systems, Chapter 22 Parenteral Nutrition, Composition of Solutions for Infants and Children, Table 22.2, page 373.

[15] ASPEN, American Society for Parenteral and Enteral Nutrition, January 18, 2019.

Per the publication by Greer et al 1988, which describes two studies in term and small pre-term infants,[16] a relatively high content of Ca and P in parenteral nutrition appears to be desirable in early infancy. Phosphorus, 40-45 mg/dL appears suitable to maintain P homeostasis. The Ca-P ratio should be 1.3 to 1 by weight or 1 to 1 by molar ratio and should be administered with an average fluid intake of ~120 to 150 mL/kg (see **Table 4**).

Table 4. Recommended intravenous intakes of phosphorus (mg/L)

Nutrient	Pre-term Infants*	Term Infant	Children > 1 yr**
	mg/L		
Phosphorus	400-450	400-450	150-300

Source: Greene et al, see footnoted reference 14 below.

*To prevent Ca-P precipitation, intakes are described per liter, to prevent administration of high concentration of Ca and P, which may result if intakes are expressed per kg body weight, and there is fluid restriction. These recommendations also assume an average e fluid intake of 120 to 150 mL kg^{-1} d^{-1} with 25 g amino acid/L of a pediatric amino acid solution. These dosage levels for preterm infants should only be given in central venous infusions.

** Requirements are less with advancing age; few data available.

See **Table 5** for serum measurements, by age, informing on Ca, P, and vitamin D homeostasis, per the Green et al (ref. 14).

Table 5. Approximate Normal Serum Ranges as a Guide to Assessment of Mineral Status

	< 2 years of age	≥ 2 years of age
Serum 25-(OH)D* nmol/L ng/L	 25-200 10-80	 25-200 10-80
Serum 1,25-$(OH)_2$** µmol/L pg/mL	 25-270 10-110	 25-90 10-50
Serum Ca*** mmol/L mg/dL	 2.25-2.62 9-10.5	 2.25-2.62 9-10.5
Serum P**** mmol/L mg/dL	 1.30-2.60 4-8	 1.15-1.95 3.5-6
Serum alkaline phosphatase (U/L)	25-250	50-200

Source: Modified from reference (ref) 10, Greene et al.

*Low levels may denote vitamin D deficiency; high levels toxicity.

**High levels may also denote Ca and/or P deficiency

***Low levels may reflect inappropriate Ca-P intake ratio.

**** Low levels reflect insufficient P intake; high levels may reflect high P intake.

Considering the route of administration and admixture procedures, the Pediatric Nutrition Handbook as well as the Greene et al[10] article recommend caution when mixing calcium and phosphorus intravenously. Care should be instituted during fluid restriction periods not to inadvertently increase the concentration of Ca and P in the total parenteral nutrition (TPN) fluid, which may result in precipitation of minerals. Factors decreasing the solubility of Ca and P are low amino acid content, low glucose content, high pH (cysteine-containing amino acid solutions are more acidic and appear to improve solubility), prolonged duration of

[16] Greer FR, Tsang RC. Calcium, phosphorus, magnesium and vitamin D requirements for the preterm infant. In: Tsang RC, ed. Vitamin and mineral requirements in preterm infants. New York: Marcel Dekker, Inc. 1985: 99-136.

intravenous tubing exposed to infant incubator air temperatures, and physiochemical factors related to mixing of chemicals (such as phosphate concentrate added to Ca-containing TPN fluid).[14] The above suggested intakes of Ca and P for pre-term infants preferably should be given through a central venous line and not in a peripheral vein. As high concentrations of Ca and P desired for the neonate may not be needed by the older pediatric patient, age-related guidelines rather than one single pediatric recommendation may be appropriate. [14]

DPMH agrees with the applicant's approach to dosing potassium phosphates injection considering the safety risks hyperkalemia and hyperphosphatemia which prompt the need for electrocardiographic (ECG) monitoring as well as careful monitoring of serum phosphorus, potassium and calcium levels during treatment. The DGIEP clinical review team concludes that the proposed formulation under NDA 212832 by Fresenius, relying on Sodium Phosphates Injection (NDA 018892 by Hospira), and Potassium Chloride (NDA 020161 by ICU Medical), will be acceptable as a source of phosphorus in intravenous fluid and for parenteral nutrition in adult and pediatric patients down to neonates based an acceptable aluminum level in this formulation as well as approved labeling of Sodium Phosphates Injection (NDA 212121) in adult and pediatric patients down to 12 years of age, based on the extensive clinical experience and the published literature submitted in the pediatric assessment under NDA 212832. See the Unireview, Section 8, Clinical Evaluation with detailed tabular summary of each publication submitted to support the new dosing regimen for pediatric patients 12 years down to neonates. See subsection 2.4 Dosage for Administration in Parenteral Nutrition, Table 2 with the recommended daily dosage of Potassium Phosphates Injection for parenteral nutrition for pediatric patients (including pre-term and term infants) and adults based on this formulation containing phosphorus 3 mmol/mL and potassium 4.4 mEq/mL (see comments later in this labeling review).

Reviewer Comments: Use of Potassium Phosphates Injection in adults and adolescents is based on FDA's findings of safety and effectiveness for Sodium Phosphates Injection (NDA 018892) with information to support that this product would deliver an equivalent amount of phosphate parenterally. DPMH agrees that efficacy can be extrapolated from adults and adolescents to younger pediatric patients including neonates, with dosing supported by published literature as well as clinical practice guidelines (under NDA 212832). The formulation under NDA 212832 for Potassium Phosphates Injection will be acceptable for use in adult patients and all pediatric ages from neonates to less than 18 years of age. Dosing will need to be adjusted based on phosphate and other relevant electrolyte needs, namely potassium and calcium. DPMH agrees with DGIEP Clinical/Clinical Pharmacology reviewers on revisions to Section 2 Dosage and Administration and subsection 2.4, Table 2 informing prescribers on the maximal daily dosage in parenteral nutrition based on clinical practice guidelines. Prescribers will be informed to individualize the dosage based upon the patient's clinical condition, nutritional requirements, and the contribution of oral or enteral phosphorus and potassium intake. Labeling will also inform prescribers that the amount of phosphorus that can be added to parenteral nutrition may be limited by the amount of calcium also added to the solution.

PREA Post Marketing Requirement

There will be no PREA PMRs for this potassium phosphates injection because Fresenius's formulation is acceptable for use in adults as well as all pediatric patients down to neonates (based on the aluminum content) and will be fully labeled under this NDA review. The substantially complete proposed labeling includes a new dosing regimen for younger pediatric patients from neonates to less than 12 years of age and the proposed dosing regimen in adults and adolescents is consistent with that approved for another Potassium Phosphates Injection product under NDA 212121.

DPMH Pediatric Labeling Recommendations

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population compared with the adult population. For products with pediatric indications, the

pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric population. The proposed indication for Fresenius's Potassium Phosphates Injection is in adults and pediatric patients down to neonates (pre-term and term infants (b) (4) as a source of phosphorus as well as for parenteral nutrition (two indications as cited earlier in this review).

As stated previously, the applicant proposes an indication across adults and all pediatric ages because the aluminum concentration is acceptable in all pediatric age groups down to neonates. Proposed labeling, submitted in the Pregnancy Lactation Labeling Rule (PLLR) format, includes indications in Section 1 for adults and pediatric patients down to neonates, Section 2 Dosage and Administration on important preparation and administration instructions as well as subsection 2.4 Dosage for Administration in Parenteral Nutrition with recommended daily dosing of Potassium Phosphates Injection for parenteral nutrition for adults and pediatric patients down to neonates. Safety risks related to administration are appropriately addressed in Section 2 and inform on the recommended rate of infusion and the need for ECG monitoring during potassium infusion. Labeling cautions not to infuse potassium phosphates with calcium containing IV fluids and consider mmol of phosphorus and mEq of potassium in the calculation of the dose and rate of administration due to the risk of hyperkalemia, Warnings and Precautions (5.3) and hyperphosphatemia and hypocalcemia (5.4). Safety risk information on aluminum toxicity appears in (5.6) and (8.4) Pediatric Use reporting on the risk of aluminum toxicity particularly in premature infants. This safety risk information appropriately cross-referenced from (8.4) with Indications and Usage (1), and Warnings and Precautions (5.3) and (5.5). There is no juvenile animal data reported in Section 8.4. See reviewer comments later in this review.

DPMH defers to DGIEP/Clinical Pharmacology and Clinical Review Team on revisions to the Indications and Usage, Dosing and Administration, and Warnings and Precautions sections to align with labeling under NDA 212121 including the well-known safety risks associated with Potassium Phosphates Injection. The Division of Pharmacovigilance (DPV) review[17] includes events of hyperkalemia, hyperphosphatemia, hypocalcemia, and aluminum toxicity as well as adverse reactions cited in labeling Section 6 Adverse Reactions. DGIEP substantially complete proposed Potassium Phosphates Injection, for IV use, labeling is dated October 8, 2019. DPMH's recommended information to be added to the labeling is underlined. Information to be deleted has a ~~strikethrough~~. Comments and rationale for DPMH's recommendations to the labeling are in *italics*.

1 INDICATIONS AND USAGE

(b) (4) Potassium Phosphates Injection (b) (4) is (b) (4) indicated 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.~~

- 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.

[17] NDA 212121 Potassium Phosphates Injection, Pharmacovigilance Review by Michelle Hines, PharmD, BCPS (dated August 13, 2019)

Reviewer Comments: DPMH recommends separating the indications into two bullets to more clearly inform prescribers on the indication for this potassium phosphates injection formulation as a source of phosphorus to correct hypophosphatemia as well as for parenteral nutrition. Labeling for this formulation will not include a Limitations of Use (as in labeling under NDA 212121) because this formulation has a low acceptable level of aluminum for use in adults as well as pediatric patients down to neonates.

2 DOSAGE AND ADMINISTRATION

2.4 Dosage for Administration in Parenteral Nutrition

(b) (4)-Potassium Phosphates Injection provides phosphorus 3 mmol/mL (potassium 4.4 mEq/mL).
The recommended daily dosage in parenteral nutrition is shown in Table 2. Individualize the dosage based upon the patient's clinical condition, nutritional requirements, and the contribution of oral or enteral phosphorus and potassium intake. The amount of phosphorus that can be added to parenteral nutrition may be limited by the amount of calcium that is also added to the solution.

TABLE 2: Recommended Daily Dosage of Potassium Phosphates Injection for Parenteral Nutrition for Pediatric Patients

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 $\geq$ 30 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2), start at the low end of the dosage range.

Monitoring
Monitor serum phosphorus, potassium, calcium and magnesium-(b) (4) concentrations and adjust the dosage accordingly.

Reviewer Comments: As of this review, these are preliminary revisions from DGIEP Clinical and Clincial Pharmacology as well as DPMH to the applicant's proposed labeling. DPMH acknowledges that there may be further revisions to Section 2.4 Recommended Dosage and Monitoring. DPMH recommends that the maximum dosage for parenteral nutrition should be clearly specified and defers to DGEIP Clinical Pharmacology on the maximum threshold of the potassium value. DPMH also recommends using weight-based dosing for pediatric patients, specifically describing dosages in mg/kg.

DPMH also recommends that prescribers be informed on the maximal dosage for this formulation for pediatric patients down to neonates. DPMH recommends to spell-out the terms, phosphorus and potassium, rather than using abbreviations and to employ units of phosphorus as millimole (mmol).

8 USE IN SPECIAL POPULATIONS

8.4 Pediatric Use

(b) (4)-

[redacted]

Safety and effectiveness of [redacted] Potassium Phosphates Injection have been established in pediatric patients as a source of phosphorus:

- in intravenous fluids to correct hypophosphatemia when oral or enteral replacement is not possible, insufficient, or contraindicated.
- for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated

Because of immature renal function, preterm infants receiving prolonged parenteral nutrition treatment with Potassium Phosphates Injection may be at higher risk of aluminum toxicity. [redacted] *[see Warnings and Precautions (5.6)]*.

Reviewer Comments: DPMH recommends cross referencing safety risk information to Section (1) Indications and Usage and Warnings and Precautions (5.6).

DPMH Actions and Labeling Recommendations

DPMH reviewed the applicant's proposed labeling for Potassium Phosphates Injection, for intravenous use and participated in meetings with the DGIEP Clinical Team from July 10, 2019 to October 22, 2019. The most recent proposed labeling revisions per DGIEP are dated October 8, 2019. DPMH labeling recommendations were provided in meeting discussions for DGIEP consideration. DPMH input will be reflected in the final labeling and the action letter from DGIEP. Final labeling will be negotiated with the applicant and may differ from comments and recommendations in this DPMH labeling review. See the **Appendix** for a summary of the information in the Unireview, Section 10 Pediatrics.

Appendix

Summary in Unireview

Under the Pediatric Research Equity Act (PREA) (21 U. S. C. 335), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable. This NDA 212832 for Potassium Phosphates Injection proposes a new dosing regimen (weight-based dosing) for pediatric patients less than 12 years of age, including neonates, and therefore, triggers PREA.

A similar Potassium Phosphates formulation (under NDA 212121 by CMP Development, Inc.) was recently FDA-approved on September 19, 2019 for adults and pediatric patients 12 years and older. Labeling for NDA 212121 Potassium Phosphates Injection is as a phosphorus replacement product indicated as a source of phosphorus;

- in intravenous fluids to correct hypophosphatemia in adults and pediatric patients 12 years of age and older when oral or enteral replacement is not possible, insufficient or contraindicated
- for parenteral nutrition in adults weighing at least 45 kg and pediatric patients 12 years of age and older weighing at least 40 kg when oral or enteral nutrition is not possible, insufficient or contraindicated.
    - Limitations of Use: Safety has not been established for parenteral nutrition in adults weighing less than 45 kg or pediatric patients less than 12 years of age or weighing less than 40 kg due to the risk of aluminum toxicity.

The NDA 212832 under this review relies on two listed products: Sodium Phosphates Injection (NDA 018892 by Hospira) a 45 mM (3 mM phosphorus/mL) which also contains 4 mEq/mL sodium and Potassium Chloride Injection (NDA 020161 by ICU Medical, Inc) as potassium 10 mEq/5 ml for single-dose infusion after dilution in a suitable large volume parenteral for treatment of potassium deficiency states when oral replacement is not feasible. Unlike the CMP product, this formulation contains an acceptable level of aluminum for all ages. Thus, NDA 212832 will be approved 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, and for parenteral nutrition in adults and pediatric patients when oral or enteral nutrition is not possible, insufficient, or contraindicated.

There is an Agreed Initial Pediatric Study Plan (iPSP), dated October 19, 2018 under IND 130166, that details a plan for submission of a pediatric assessment based on adult-to-pediatric extrapolation of efficacy using published literature findings to support the two proposed indications (e.g., as a source of phosphorus for correcting or preventing hypophosphatemia and/or as an additive to parenteral fluid formulas).

The applicant relies on published literature for extrapolation from adult data based on extensive clinical experience with the dosing regimen for sodium phosphates and potassium phosphates injection. There are no adequate and well-controlled clinical studies in pediatric patients. Phosphorus dosing to correct hypophosphatemia and for use in total parenteral nutrition (TPN) requirements in pediatric patients (including neonates) are described in clinical practice guidelines for parenteral nutrition formulation recommendations. The safety risks of hyperkalemia, hyperphosphatemia, and hypocalcemia are similar to adults.

Section 8.4 (Pediatric Use) will reflect that safety and effectiveness of POTASSIUM PHOSPHATES Injection have been established in pediatric patients as a source of phosphorus to correct hypophosphatemia and that safety and effectiveness of POTASSIUM PHOSPHATES have been established for parenteral nutrition in all pediatric patients down to neonates. A separate Division of Pediatric and Maternal Health (DPMH) Labeling Review is in the Document Archiving, Reporting and Regulatory Tracking System (DARRTS).

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CAROLYN L YANCEY
10/24/2019 12:16:36 PM

JOHN J ALEXANDER
10/24/2019 01:36:01 PM
Also signing for Dr. Hari Sachs

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

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

Date of This Review:	October 15, 2019
Requesting Office or Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Application Type and Number:	NDA 212832
Product Name and Strength:	Potassium Phosphates Injection, USP phosphorus 15 mmol/5 mL (3 mmol/mL) and Potassium 22 mEq/5 mL (4.4 mEq/mL) Phosphorus 45 mmol/15 mL (3 mmol/mL) and Potassium 66 mEq/15 mL (4.4 mEq/mL) Phosphorus 150 mmol/50 mL (3 mmol/mL) and Potassium 220 mEq/50 mL (4.4 mEq/mL)
Total Product Strength:	Phosphorus 15 mmol and Potassium 22 mEq per 15 mL Phosphorus 45 mmol and Potassium 66 mEq per 15 mL Phosphorus 150 mmol and Potassium 220 mEq per 50 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Fresenius Kabi USA, LLC
FDA Received Date:	May 29, 2019, July 11, 2019 and July 18, 2019
OSE RCM #:	2019-1135
DMEPA Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Idalia E. Rychlik, Pharm.D.

1 REASON FOR REVIEW

As part of the approval process for Potassium Phosphates Injection, USP, the Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that we review the proposed potassium phosphates injection, USP prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 BACKGROUND

NDA 212832 is a 505(b)(2) NDA and the listed drug products are Hospira's sodium phosphates injection USP, 3 mmol phosphate/mL (NDA 18892) 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 (NDA 20161).

3 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
FDA Adverse Event Reporting System (FAERS)*	C-N/A
Information Request	D
Labels and Labeling	E

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI), container labels, and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Gastroenterology and Inborn Errors Products (DGIEP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	We note that the proposed product is indicated for pediatric	Absence of pediatric patient dosing for the indicated	We defer to DGIEP to add the omitted pediatric dosing information.

Table 2. Identified Issues and Recommendations for Division of Gastroenterology and Inborn Errors Products (DGIEP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	patients, but the pediatric dosing information is absent.	pediatric patient population may result in dosing errors.	
2.	The package type terminology for the 50 mL presentation is incorrect.	We note, the Applicant's response dated August 21, 2019, to our Information Request sent on August 20, 2019. The Sponsor clarified that the 50 mL vial presentation is intended to be used solely as a Pharmacy Bulk Package (PBP). The current package type terminology is inconsistent with Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use.	We defer to Office of Pharmaceutical Quality (OPQ) to add the appropriate package type term. (See Appendix D).
3.	The product element name within the strength statement is inconsistent with the Reference Listed Drug's (RLD); the product element is presented as (b) (4) on the proposed label and labeling versus "phosphorous" for the RLD.	Inconsistencies between product element terminology within the strength statement can cause confusion and lead to medication dose errors.	Revise the product's elemental name/description in the strength statement to align with the RLD (e.g. phosphorous).
Full Prescribing Information – Section 2 Dosage and Administration			
1.	Use of confusing symbols (e.g., "<", ">", "-") are	These symbols may be mistaken as opposite of the intended meaning. The	Replace the symbols "<" and ">", and "-"with their intended meaning.

Table 2. Identified Issues and Recommendations for Division of Gastroenterology and Inborn Errors Products (DGIEP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	noted under sections 2.1 and 2.2.	usage of symbols can cause misinterpretation and confusion.[1]	
2.	Numeric values, found in Table 1 of Section 2.2, are missing their corresponding units of measure.	The absence of defined units of measure in a dosing table may lead to confusion and medication dose errors.	Revise the dose ranges located in Table 1, Section 2.2 to include a unit of measure after each numeric. For example, 0.16 mmol/kg to 0.32 mmol/kg
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	Appropriate description of product characteristics important to facilitate identification of the product dosage form are missing.	Per CFR 201.57(c)(4)(ii), this information is necessary to facilitate identification of the dosage form.	For parental dosage forms (e.g., injection) include information about color (e.g., clear solution) and other identifying characteristics to help facilitate product identifications and mitigate the potential use of adulterated product.
2.	The presentation of product strength is omitted.	21 CFR 201.15(a)(6)	Ensure all intended product strengths are listed in Section 3: Dosage Forms and Strengths.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	This section is missing important product identifying characteristics such as the color.	This information is necessary to facilitate identification of the dosage form.	Add the color and any other pertinent identifying characteristics of the solution.

[1] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2015 Sep 16]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

Table 2. Identified Issues and Recommendations for Division of Gastroenterology and Inborn Errors Products (DGIEP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	The concentration of potassium and phosphorous are presented in terms of XX mmol per 1 mL or XX mEq per 1 mL.	USP General Chapter <7> Labeling.	Revise the concentrations of phosphorous and potassium to read xx mmol/mL or xx mEq/mL in accordance with USP General Chapter <7>.

Table 3. Identified Issues and Recommendations for Fresenius Kabi USA, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling			
1.	The package type term for the 50 mL vial is incorrect.	We note, your response dated August 21, 2019, to our Information Request sent on August 20, 2019; the 50 mL vial presentation is intended to be used solely as a Pharmacy Bulk Package (PBP). The current package type terminology is inconsistent with Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use.	Revise the package type term on the carton labeling and container label from (b) (4) to "Pharmacy Bulk Package – Not for Direct Infusion".
2.	There is inadequate differentiation between the Pharmacy Bulk Package and Single-Dose Vial label and labeling.	The proposed Pharmacy Bulk Package presentation contains an excess drug volume of 33 mL. This excessive volume may lead to dosage and administration medication	Consider the use of different colors, boxing, or some other means to provide adequate differentiation between the container labels and carton labeling for the Pharmacy Bulk

Table 3. Identified Issues and Recommendations for Fresenius Kabi USA, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		errors, such as patient over-dose in the event the PBP is mistaken for the single dose vial presentations.	Package and Single dose vial presentations.
3.	The product's element name within the strength statement is inconsistent with the Reference Listed Drug's (RLD); the product element is presented as (b) (4) on the proposed label and labeling verses "phosphorous" for the RLD.	Inconsistencies between product element terminology within the strength statement can cause confusion and lead to medication dose errors.	Revise the product's elemental name/description in the strength statement to align with the RLD (e.g. phosphorous).
4.	As currently displayed, the element names, (b) (4)	Lack of clarity.	Revise the strength presentation so that the "Phosphorus" and "Potassium" appear before the amount of each element. This follows the typical format of "name then strength" for prominent strength expressions. For example, Phosphorous 15 mmol/5 mL (3 mmol/mL) Potassium 22 mEq/5 mL (4.4 mmol/mL)
5.	Most of the strength statements have additional space (s) before and/or after the slash mark ("/") sign.	The additional spaces in the strength statement may diminish the readability.	Delete the extra space (s) before and after the slash mark sign in the strength statements. For example,

Table 3. Identified Issues and Recommendations for Fresenius Kabi USA, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			phosphorus 15 mmol/5 mL
6.	The route of administration (ROA) is presented as an abbreviation, (e.g. (b) (4)) and important administration warnings are omitted from the ROA statement.	Per our Draft Guidance: Container and Carton, April 2013 (line 479) route of administration should be expressed in as a non-abbreviated statement. Furthermore, omitting product administration warnings may lead to medication administration errors.	Revise the route of administration statement from (b) (4) to read "For intravenous infusion (b) (4) only".
7.	The principal display panel (PDP) is missing the cautionary statement "Must dilute before use".	A cautionary statement for dilution is intended to prevent a medication administration error and/or patient adverse event if the injectable drug is used inappropriately.	Add the statement "Must dilute before use" on the principal display panel to minimize the risk of the product being administered without dilution.
8.	The net quantity statement is overly prominent and takes the reader's attention away from more important product information, such as the product strength.	Post-marketing experience shows that the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is more prominent.	Decrease the prominence of net quantity statement.
9.	The 5 mL and 15 mL vial presentations contain more drug than needed to provide the dose listed in the Dosage and Administration section of the PI.	In order to minimize the risk of the entire contents of the vial being given as a single dose, appropriate package type terms and instruction should be utilized.	Revise the statement (b) (4) to read "Single-Dose Vial – Discard Unused Portion".
10.	Usual Dosage statement terminology is inconsistent with that	21 CFR 201.55	To ensure consistency with the Prescribing Information, revise the statement, (b) (4) to read

Table 3. Identified Issues and Recommendations for Fresenius Kabi USA, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	used in the Prescribing Information.		"Recommended Dosage: See Prescribing Information."
11.	Negative statement "Contains no more than 2,000 mcg/L of aluminum." is identified.	Due to our understanding of post-marketing reports, negative statements may have the opposite of intended meaning because the word 'not' can be overlooked and the warning be misinterpreted as an affirmative action.[2]	Consider revising the aluminum content statement to read "Contains 2,000 mcg/L or less of aluminum".
12.	The lot number statement and the expiration date statement ("LOT/EXP") are on the same line.	The lot number statement should be clearly differentiated from the expiration date statement.[3]	Revise the lot number statement and expiration date statement ("LOT/EXP") to ensure they are on separate lines. For example, LOT: EXP:
13.	It is unclear what the intended meaning of the placeholder (XXXXXX) located immediately above the lot and expiration date statements (LOT/EXP).	The close proximity of an undefined code near the lot number statement or expiration date statement may lead to numerical confusion.	Define the meaning of the undefined code (XXXXXX) located immediately above the lot and expiration date statements (LOT/EXP). If it is an internal code, relocate to a different location away from other important product information.
14.	The diluted or admixed storage information is missing.	The diluted or admixed storage information minimizes the risk of	Include storage information for diluted or admixed product.

[2] Institute for Safe medication practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Safe Alert Acute Care. 2010;15(16):1-3.

[3] Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Safe Alert Acute Care. 2014;19(23):1-4.

Table 3. Identified Issues and Recommendations for Fresenius Kabi USA, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		administering expired products.	
15.	The human readable product identifier required under the Drug Supply Chain Security Act (DSCSA) is incomplete, the serial number is omitted. Additionally, it is unclear where the machine-readable product identifier is located on the label.	The Drug Supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest saleable unit display a human-readable and machine-readable (2D data matrix barcode) product identifier.	The DSCSA guidance on product identifiers recommends the format below for the human-readable portion of the product identifier. The guidance also recommends that the human-readable portion be located near the 2D data matrix barcode. NDC: [insert NDC] SERIAL: [insert serial number] LOT: [insert lot number] EXP: [insert expiration date] We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf.
16.	The format for expiration date is undefined.	The expiration date should be clearly defined to minimize confusion and risk for deteriorated drug medication errors.	Submit expiration date in the format that is stated below. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used

Table 3. Identified Issues and Recommendations for Fresenius Kabi USA, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
17.	The abbreviation "q.s." is identified.	The usage of abbreviation can cause misinterpretation and confusion.	Replace the abbreviation with its intended meaning.
Container Labels			
1.	It is unclear if the linear barcode on the container label is scannable when placed around the curvature of the vial.	The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature.	Verify that the linear barcode on the container label is scannable when placed around the curvature of the vial.

5 CONCLUSION

Our evaluation of the proposed potassium phosphates injection, USP prescribing information (PI), container labels, and carton labeling for identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Fresenius Kabi USA, LLC so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for potassium phosphates injection, USP that Fresenius Kabi USA, LLC submitted on May 29, 2019.

Table 4. Relevant Product Information for potassium phosphates injection, USP	
Initial Approval Date	N/A
Active Ingredient	potassium phosphates
Indication	(b) (4) [redacted]
Route of Administration	intravenous
Dosage Form	injection
Strengths	phosphorous 15 mmol/5 mL (phosphorous 3 mmol /mL), phosphorous 45 mmol /15 mL (phosphorous 3 mmol /mL), and phosphorous 150 mmol /50 mL (phosphorous 3 mmol /mL)
Dose and Frequency	(b) (4) [redacted]
How Supplied	5 mL single dose vial, 15 mL single dose vial and 50 mL pharmacy bulk package.
Storage	Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 20, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, potassium phosphates. Our search identified one previous review[d] and we confirmed that our previous recommendations were implemented.

APPENDIX D: INFORMATION REQUEST

Quality information amendment was submitted on August 21, 2019:

Link to the submission:

\\cdsesub1\evsprod\nda212832\0006\m1\us\12-cover-letter\cover-letter.pdf

In your submission dated, May 29, 2019 (Module 3.2.P.2 Elemental Impurity Assessment Summary), you stated that the Maximum Daily Volume (MDV) for Potassium Phosphates Injection, USP is 17 mL/day. Additionally, we understand the proposed product will be provided as a 50 mL, single-dose vial without preservatives; we note the proposed product presentation contains an excess drug volume of 33 mL. We are concerned that this excessive volume may lead to dosage and administration medication errors, such as patient over-dose. Please explain how the 50 mL, single-dose presentation is intended to be used in the clinical setting and your plans to mitigate the medication administration and dosing errors which could result from the excess drug volume.

Based on the current usage of the marketed unapproved drug product, the 50 mL presentation is intended to be used in the clinical setting as a Pharmacy Bulk Package (PBP). As defined in USP <659> and based on the current usage of the unapproved product, the 50 mL PBP presentation will be used as follows: "(b) (4) *Closure* (b) (4) only one time with a suitable sterile transfer device or dispensing set that allows measured dispensing of the contents". For example, the 50 mL presentation would be used in the compounding pharmacy by withdrawing the entire vial contents in a single step to then prepare 5 separate admixtures, single doses, at the commonly used dose of 30 mmol (10 mL/dose). To mitigate potential medication administration and dosing errors the container and carton labeling, as well as the impacted sections of the prescribing information (package insert), will be revised accordingly.

[d] Abraham, S. Label and Labeling Review for Potassium Phosphates for Injection (NDA 212121). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Jul 15. RCM No.: 2019-685.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following potassium phosphates injection, USP labels and labeling submitted by Fresenius Kabi USA, LLC.

- Container labels received on May 29, 2019
- Carton labeling received on May 29, 2019
- Prescribing Information (Image not shown) received on May 29, 2019
  \\cdsesub1\evsprod\nda212832\0001\m1\us\114-labeling\114a-draft-label\fkusa-draft-pi-word.docx

F.2 Label and Labeling Images

Container labels:

(b) (4)

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

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/s/

SHERLY ABRAHAM
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10/15/2019 12:14:41 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Review

Date:	September 13, 2019
Reviewer:	Michelle Hines, PharmD, BCPS Division of Pharmacovigilance I (DPV-I)
Medical Officer:	Paolo Fanti, MD DPV-I
Team Leader:	Lisa Harinstein, PharmD, BCCCP DPV-I
Deputy Division Director:	Monica Muñoz, PharmD, PhD, BCPS DPV-I
Product Name:	Potassium phosphates injection
Subject:	All adverse events
Application Type/Number:	NDA 212832
Applicant:	Fresenius Kabi USA, LLC
OSE RCM #:	2019-1257

TABLE OF CONTENTS

1 INTRODUCTION

This review, completed by the Division of Pharmacovigilance I (DPV-I) in response to a consult from the Division of Gastroenterology and Inborn Errors Products (DGIEP), contains an evaluation of the FDA Adverse Event Reporting System (FAERS) database for all adverse event reports with potassium phosphates injection and sodium phosphates injection through April 22, 2019. This review will inform DGIEP as they determine the acceptability of product labeling submitted for NDA 212832 potassium phosphates injection.

Throughout this review, we use intravenous (IV) potassium phosphates to describe IV administration of diluted *or* undiluted potassium phosphates injection; we use potassium phosphates injection to specifically describe administration of undiluted potassium phosphates injection.

1.1 BACKGROUND AND REGULATORY HISTORY

On May 29, 2019, the applicant submitted NDA 212832 for potassium phosphates injection, USP; 3 millimoles (mmol) phosphate and 4.4 milliequivalents (mEq) potassium per milliliter (mL), 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. NDA 212832 was submitted as a 505(b)(2) application with sodium phosphates injection (sponsor Hospira Inc.; NDA 018892; approved on May 10, 1983) and potassium chloride injection (sponsor ICU Medical Inc.; NDA 020161; approved on November 30, 1992) as the Orange Book Reference Listed Drugs (RLD).

Potassium phosphates injection is included on the Institute for Safe Medication Practices (ISMP) list of high-alert medications in acute care settings.[1] High-alert medications are drugs that have a heightened risk of causing significant patient harm when used in error. Potassium phosphates injection contains 4.4 milliequivalents (mEq) potassium/mL, whereas concentrated potassium chloride injection contains 2 mEq potassium/mL—potassium phosphates injection contains more than double the amount of potassium/mL compared to potassium chloride injection.

On May 31, 2019, DGIEP consulted DPV-I to provide an assessment of adverse events reported to the FAERS database with marketed, unapproved formulations of potassium phosphates injection and the RLDs. On August 13, 2019, DPV-I completed a separate review of postmarketing adverse events reported with potassium phosphates injection and sodium phosphates injection (RLD) for NDA 212121, which is a separate application for potassium phosphates injection currently under FDA review. This current review will use the same case series of adverse events with potassium phosphates to inform the appropriateness of adverse events included in the proposed labeling for NDA 212832.

1.2 PROPOSED LABELING FOR POTASSIUM PHOSPHATES INJECTION FROM JULY 18, 2019

The applicant identified the terms listed in the ADVERSE REACTIONS section of the proposed labeling for potassium phosphates injection from the *literature* only.[a] The WARNINGS AND PRECAUTIONS (highlights),[b] ADVERSE REACTIONS (verbatim) section, and one portion of the DRUG INTERACTIONS section of the most recent version (submitted on July 18, 2019) of the proposed potassium phosphates injection labeling are reproduced below. **Appendix A** includes the full WARNINGS AND PRECAUTIONS and OVERDOSAGE sections.

Of note, the ADVERSE REACTIONS section is separated into events associated with 1) intravenous phosphate administration, 2) combined potassium and phosphate intoxication from overdose, or 3) excessive doses of intravenous phosphate.

----------WARNINGS AND PRECAUTIONS----------

(b) (4)

6 ADVERSE REACTIONS

(b) (4)

[a] In contrast, the applicant for NDA 212121, the other potassium phosphates injection application currently under FDA review, provided postmarketing adverse event reports in addition to literature references in support of proposed adverse events for labeling.

[b] The applicant's proposed labeling from July 18, 2019, also includes warnings for *Aluminum Toxicity (5.6)* and (b) (4) *(5.7)*; however, these are not listed in HIGHLIGHTS OF PRESCRIBING INFORMATION.

(b) (4)

7 DRUG INTERACTIONS

(b) (4)

2 METHODS AND MATERIALS

2.1 CASE SELECTION CRITERIA

We searched for reports that described adverse events following administration of IV potassium phosphates or sodium phosphates. We determined whether an adverse event was associated with usual or inappropriate use by comparing the case details to the proposed labeling for potassium phosphates injection.

We excluded reports that did not describe IV administration of potassium phosphates or sodium phosphates to a patient.

2.2 FAERS DATABASE SEARCH STRATEGY

DPV-I searched the FAERS database for all adverse events with potassium phosphates injection (Search 1) or the RLD,[c] sodium phosphates injection (Search 2), with the broad search strategy described in **Table 1**.[d]

Table 1. FAERS Search Strategy*		
	Search 1	**Search 2**
Date of search	April 23, 2019	

[c] We applied the same case series described in our review of potassium phosphates injection for NDA 212121; this review did not include a search for adverse events with potassium chloride injection. However, the case series reflects safety issues associated with potassium chloride injection, therefore we did not expand our search for the current review.

[d] Of note, this broad search strategy captured reports with other products containing potassium phosphates or sodium phosphates and other dosage forms of these products that were not informative for our review of injectable potassium or sodium phosphates.

Table 1. FAERS Search Strategy*		
	Search 1	**Search 2**
Time period of search	All reports through April 22, 2019	
Search type	Quick Query	
Product Active Ingredients	POTASSIUM PHOSPHATE; POTASSIUM PHOSPHATE, DIBASIC; POTASSIUM PHOSPHATE, DIBASIC\POTASSIUM PHOSPHATE, MONOBASIC; POTASSIUM PHOSPHATE, MONOBASIC; POTASSIUM PHOSPHATE, UNSPECIFIED FORM	SODIUM PHOSPHATE, DIBASIC;SODIUM PHOSPHATE, DIBASIC, ANHYDROUS\SODIUM PHOSPHATE, DIBASIC, HEPTAHYDRATE\SODIUM PHOSPHATE, MONOBASIC, MONOHYDRATE; SODIUM PHOSPHATE, DIBASIC, ANHYDROUS; SODIUM PHOSPHATE, DIBASIC, ANHYDROUS\SODIUM PHOSPHATE, MONOBASIC; SODIUM PHOSPHATE, DIBASIC, ANHYDROUS\SODIUM PHOSPHATE, MONOBASIC, ANHYDROUS; SODIUM PHOSPHATE, DIBASIC, ANHYDROUS\SODIUM PHOSPHATE, MONOBASIC, MONOHYDRATE; SODIUM PHOSPHATE, DIBASIC, HEPTAHYDRATE\SODIUM PHOSPHATE, MONOBASIC; SODIUM PHOSPHATE, DIBASIC, DIHYDRATE\SODIUM PHOSPHATE, MONOBASIC, MONOHYDRATE; SODIUM PHOSPHATE, DIBASIC, HEPTAHYDRATE\SODIUM PHOSPHATE, MONOBASIC, MONOHYDRATE; SODIUM PHOSPHATE, DIBASIC, MONOHYDRATE; SODIUM PHOSPHATE, DIBASIC\SODIUM PHOSPHATE, DIBASIC, DODECAHYDRATE; SODIUM PHOSPHATE, DIBASIC\SODIUM PHOSPHATE, MONOBASIC; SODIUM PHOSPHATE, DIBASIC\SODIUM PHOSPHATE, MONOBASIC, ANHYDROUS;SODIUM PHOSPHATE, MONOBASIC; SODIUM PHOSPHATE, MONOBASIC, ANHYDROUS; SODIUM PHOSPHATE, MONOBASIC, MONOHYDRATE; SODIUM PHOSPHATE, MONOBASIC, UNSPECIFIED FORM; SODIUM PHOSPHATE\SODIUM PHOSPHATE, DIBASIC; SODIUM PHOSPHATE\SODIUM PHOSPHATE, DIBASIC, ANHYDROUS;SODIUM PHOSPHATE\SODIUM PHOSPHATE, MONOBASIC; SODIUM PHOSPHATE\SODIUM PHOSPHATE, MONOBASIC, UNSPECIFIED FORM
* See **Appendix B** for a description of the FAERS database.		

2.3 CAUSALITY ASSESSMENT

Reports from the FAERS database search meeting the above case selection criteria were assessed for a causal relationship between the adverse event and potassium phosphates injection or sodium phosphates injection using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) system as shown below in **Table 2**. We excluded cases that we assessed as "unlikely" or "unassessable."

Table 2. Causality Classification and Criteria Based on the WHO-UMC System	
Causality Term	**Assessment Criteria**
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary

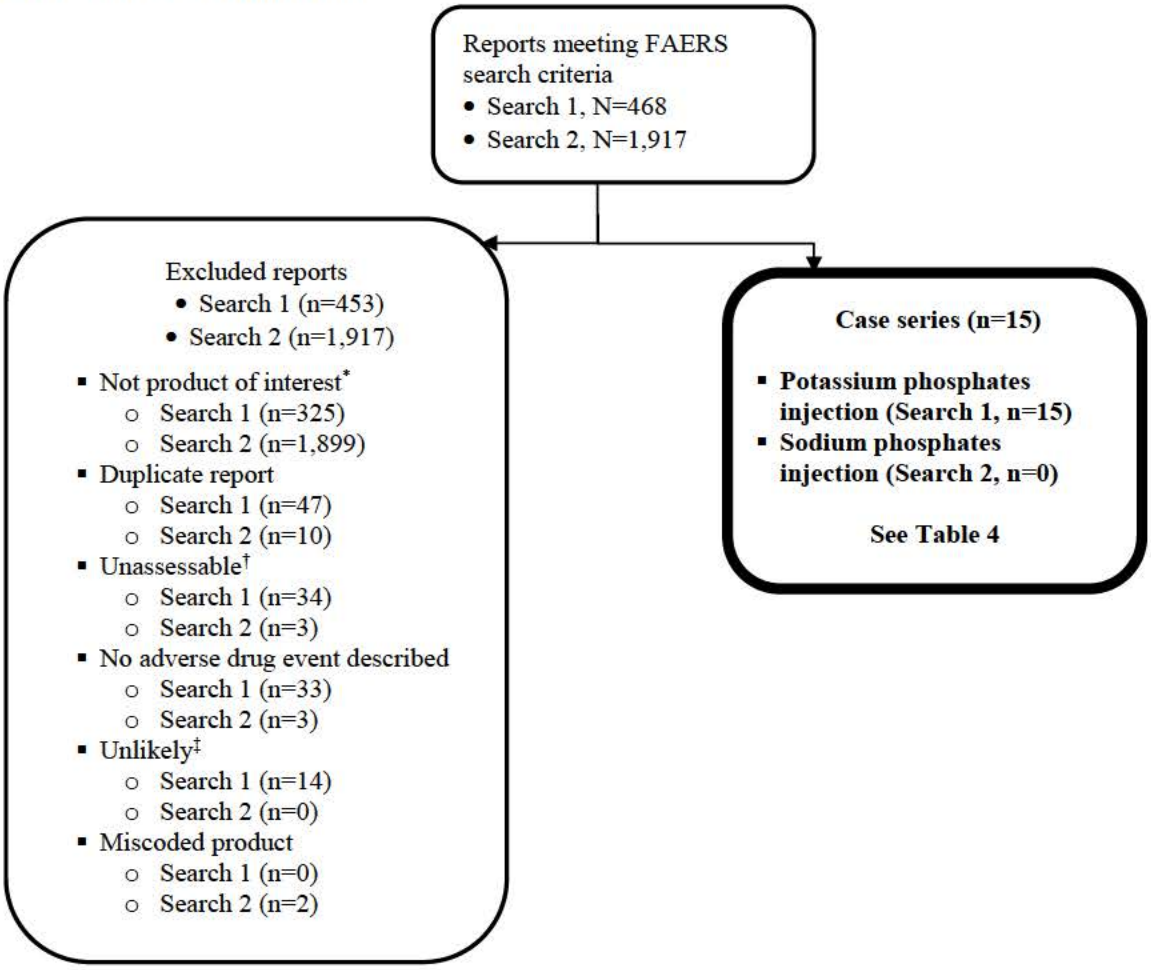
Table 2. Causality Classification and Criteria Based on the WHO-UMC System	
Causality Term	**Assessment Criteria**
Probable	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanation
Unassessable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

3 RESULTS

3.1 FAERS CASE SELECTION

Our searches of the FAERS database for reports with unapproved potassium phosphates injection (Search 1) or sodium phosphates injection (Search 2) retrieved 468 and 1,917 reports, respectively. After removing reports with non-injectable potassium phosphates- or sodium phosphates-containing products, accounting for duplicate reports, removing reports that did not describe IV administration to a patient, and performing causality assessment per **Section 2.3**, we identified 15 cases of adverse events with potassium phosphates injection and zero cases with sodium phosphates injection use (see **Figure 1**).

Figure 1. FAERS Case Selection



* Reports that did not describe the product of interest may contain duplicate reports.
† Reports had limited information to assess causality or to determine the product dosage form.
‡ Reports were unlikely to have a causal association with potassium phosphates injection or sodium phosphates injection.

3.2 FAERS DATA SUMMARY

Our case series includes 15 adverse event cases with potassium phosphates injection from the FAERS database; of these, 14 resulted from inappropriate administration.[e] We describe the adverse events reported to the FAERS database associated with IV potassium phosphates administration in our case series in **Sections 3.2.1** and **3.2.2**.

The descriptive characteristics of the 15 cases are summarized in **Table 3** below. **Appendix C** contains a line listing of cases included in the case series.

[e] The Division of Medication Error Prevention and Analysis provides a separate analysis of cases that describe medication errors with IV potassium phosphates in their review of NDA 212121.

Table 3. Descriptive Characteristics of Cases of Adverse Events with Potassium Phosphates Injection Use in the FAERS Database, Received by FDA Through April 22, 2019	
	(N=15)
Country	
United States	13
Foreign	2
Age (years)	
<1 – <17	1
17 – <65	7
≥65	3
Not reported	4
Sex	
Female	4
Male	7
Not reported	4
Serious outcomes*	(n=12)
Death	6†
Life-threatening	4
Other serious event	2
Hospitalized	1
Required intervention	1
Initial FDA received year	
1990 – 1999	3
2000 – 2009	10
2010 – 2019	2
Event associated with inappropriate administration or usual use‡	
Inappropriate administration	14
Usual use	1
WHO-UMC causality category	
Probable	13
Possible	2

* A serious adverse drug experience per regulatory definition (CFR 314.80) includes outcomes of: death, life-threatening, hospitalization, disability, congenital anomaly, required intervention, or other serious important medical events. A case can have one or more outcomes.
† One additional case of death was from a reporter requesting compatibility information who described a patient who died following potassium phosphates administration; this case had a non-serious outcome.
‡ As assessed per DPV-I reviewer

3.2.1 Case of Adverse Event with Usual Use of IV Potassium Phosphates (n=1)

One serious case describing the adverse events acute phosphate nephropathy and nephrocalcinosis associated with potassium phosphates injection use is summarized below.

FAERS case 7098986, other serious outcome, United States, 2009: A case in the published medical literature[2] describes a 30-year-old female organ donor who presented to the emergency department in diabetic ketoacidosis, with severe headache, nausea, mental status change,

tachypnea, and slurred speech. Following a seizure episode lasting for 13 minutes, the donor was intubated and admitted to the intensive care unit. A computed tomography scan of the head revealed cerebral edema, ischemic infarction of both hemispheres, and an old subarachnoid hemorrhage. Twelve hours following admission, her first recorded serum phosphate level was 1.0 milligrams (mg)/deciliter (dL). Over the next 2 days, she received 120 millimoles of intravenous phosphate as potassium phosphates; 60 hours after admission, her serum phosphorus level was 3.9 mg/dL and the phosphorus infusion was discontinued. On day 5 of hospitalization, brain flow study was consistent with brain death, and her organs, including kidneys, were procured for transplantation. Around the time of organ procurement, the donor's serum phosphorus had risen to 6.2 mg/dL, serum calcium declined to 5.8 mg/dL, and serum creatinine was 1.4 mg/dL (1.7 mg/dL at admission, with improvement to 0.9 mg/dL by hospital day 2); the final serum creatinine was 1.7 mg/dL. Because the donor had a history of diabetes, both donor kidneys underwent postprocurement biopsy, which revealed numerous intratubular calcium phosphate deposits. Serial kidney biopsies performed on each of the donated kidneys starting two weeks after transplantation showed no evidence of acute rejection but revealed persistent intratubular deposition of microcrystals that strongly stained black with Von Kossa stain, consistent with calcium phosphate crystal deposits (Figure 1A, B).

Medical officer's (nephrologist) comment: This case describes acute phosphate nephropathy with renal tubular deposition of calcium/phosphorus products (nephrocalcinosis) probably associated with administration of potassium phosphates injection. The applicant's proposed labeling lists nephrophathy; the event described in this case is more specifically described by the term "acute phosphate nephropathy."

3.2.2 Cases of Adverse Events with Inappropriate Administration of IV Potassium Phosphates or Potassium Phosphates Injection (n=14)

We identified 14 adverse event cases associated with IV administration of precipitated calcium/phosphates admixture, rapid administration of IV potassium phosphates (undiluted or diluted), or overdose—the events and serious outcomes, including deaths, described in these cases were not associated with usual administration/use of IV potassium phosphates.

These 14 cases and the DPV-I reviewer's comments related to the applicant's proposed labeling are summarized in **Table 4** below.

Table 4. DPV-I Reviewer Assessment* of Adverse Event Terms Associated with Inappropriate Administration of Potassium Phosphates Injection (N=14)			
Category	**FAERS Case Numbers**	**Summary of Cases**	**Reviewer's Comment**
IV administration of precipitated calcium/potassium phosphates admixture (n=4)	4148591, 6012327, 6339307, and 3218063	• Cases described IV administration of admixtures containing precipitated calcium/potassium phosphates • 3 cases resulted in death • Cases encompass the following events: cardiac arrest, dyspnea	• The proposed labeling does *not* currently include a warning for risk of death due to pulmonary vascular precipitates • These cases support an association between cardiac arrest and dyspnea and inappropriate IV administration of precipitated calcium/potassium phosphates admixture
Rapid IV administration of potassium phosphates (n=6)	3714869, 4031331, 5696185, 11232097, 4139567, and 3720793	• Cases had outcomes of death (n=2), cardiac arrest (n=4), life-threatening (n=1), or need for "resuscitation" (n=1) • Of the 6 cases, 5 involved rapid "IV push" administration of concentrated/undiluted potassium phosphates injection; of these, 2 cases involved accidental administration due to confusion of potassium phosphates injection with a heparin flush, and in 4 cases undiluted potassium phosphates injection was present in a patient care area or at the patient's bedside • 4 of the 5 cases with IV push administration reported the quantity of potassium phosphates administered; these ranged from 15 mmol phosphate/22 mEq potassium to 45 mmol phosphate/66 mEq potassium • 1 patient received 30 mmol phosphate/44 mEq potassium IV over 1 hour; 1-2 hours after completion of the infusion, his serum potassium level increased from 3.7 to 7.1 (units not provided), serum phosphorus increased from 0.8 to 2.5 (units not provided), and heart rate decreased from 80 beats per minute (bpm) to 50 bpm. The patient required treatment for hyperkalemia, external pacing for bradycardia, and IV vasopressors for hypotension and recovered the following day. • Cases encompassed the following events: bradycardia, cardiac arrest, hyperkalemia,	• These cases support an association between bradycardia, cardiac arrest, cardiac arrhythmia, hyperkalemia, and hypotension and inappropriate IV administration of potassium phosphates • One case had bradycardia and hypotension in the setting of potassium intoxication following IV administration of potassium phosphates

Table 4. DPV-I Reviewer Assessment* of Adverse Event Terms Associated with Inappropriate Administration of Potassium Phosphates Injection (N=14)			
Category	**FAERS Case Numbers**	**Summary of Cases**	**Reviewer's Comment**
		hypotension, and ventricular fibrillation (cardiac arrhythmia) • All cases administered potassium phosphates injection faster than recommended in the proposed DOSAGE AND ADMINISTRATION section	
Overdose (n=3)	6212975, 4009998, and 5689111	• 2 cases had an outcome of death • Cases encompass the following events: cardiac arrest, cardiac arrhythmia, hyperphosphatemia, and muscle spasm • 1 patient was ordered to receive 100 mmol phosphates and 94 mEq potassium via TPN over an unreported duration of time upon hospital discharge. Six days later, the patient experienced lower extremity cramping, and muscles "locking up", and had the following laboratory derangements (units and patient's baseline values not provided): blood urea nitrogen, 86; serum creatinine, 8.2; phosphorus, 13.4. • 1 patient received 273 mmol phosphates and 400 mEq potassium over 3 hours and died • 1 infant received 17.4 mmol phosphates and 25.5 mEq potassium over an unreported duration of time and died	These cases support an association between cardiac arrest, cardiac arrhythmia, hyperphosphatemia, and tetany with *overdose* of IV potassium phosphates. The case details are insufficient to determine whether the patient's lower extremity cramping tetany are related to (presumed) hypocalcemia or uremia.
Adverse event with unclear administration (n=1)†	14549256	• A 1-year-old infant received intravenous potassium phosphates injection "for a medical procedure which lasted for 5.0 minutes"; he "was given an incorrect route of drug administration" and developed hyperkalemia, hyperphosphatemia, and cardiac arrest • Case had an outcome of death • Case included limited information to describe the nature of maladministration of potassium phosphates injection	This case supports an association between cardiac arrest, hyperkalemia, and hyperphosphatemia with *inappropriate IV administration* of potassium phosphates.

* DPV-I reviewer assigned each case to one of four categories that describes the administration or dosing associated with the reported adverse events.
† This case may represent an additional case of rapid IV administration of potassium phosphates; however, there is limited information to include this case in that category.

4 DISCUSSION

The purpose of this review is to determine the acceptability of terms that the applicant included in the proposed ADVERSE REACTIONS section of the potassium phosphates injection labeling based on reports with IV administration of marketed, unapproved formulations of potassium phosphates injection or sodium phosphates injection (i.e., one of the RLDs for NDA 212832, a 505(b)(2) application). On August 15, 2019, DPV-I completed a review that described 15 adverse event cases from the FAERS database with IV potassium phosphates to inform DGIEP's review of NDA 212121, which is a separate application for potassium phosphates injection; NDA 212121 did not list potassium chloride injection as a RLD, therefore we did not include potassium chloride injection in our FAERS database search strategy. We used this same case series to inform our review of adverse events included in the proposed labeling for NDA 212832. Of the 15 cases in our case series, 14 involved improper administration of potassium phosphates injection, and 1 adverse event occurred with usual use.

Of note, the ADVERSE REACTIONS section (b) (4) Our case series describes clinically significant adverse events that are specific to the way that potassium phosphates injection was administered. (b) (4)

DPV-I identified one postmarketing case that described the events nephrocalcinosis and acute phosphate nephropathy that had a probable causal association with usual administration of IV potassium phosphates in the FAERS database. The applicant's proposed ADVERSE REACTIONS section of the labeling lists nephrocalcinosis and renal failure, (b) (4) as events associated with IV phosphate administration. We recommend the addition of "acute phosphate nephropathy" to the portion of the ADVERSE REACTIONS section of the labeling specific to IV phosphate administration to provide a specific description of the nephropathy associated with phosphate administration.

Our case series supports an association between inappropriate IV administration or overdosage of potassium phosphates and the following adverse events: bradycardia, cardiac arrest, cardiac arrhythmia, dyspnea (following IV administration of precipitated calcium/potassium phosphates admixture, discussed below), hyperkalemia, hyperphosphatemia, tetany, and hypotension. The applicant's proposed ADVERSE REACTIONS section of the labeling appropriately lists hyperkalemia, hyperphosphatemia, (b) (4) arrhythmia, hypocalcemic tetany, and hypotension. DPV-I recommends the addition of the following terms to the portion of the ADVERSE REACTIONS section describing adverse events with combined potassium and phosphate intoxication based on our case series: bradycardia and cardiac arrest. The applicant's proposed OVERDOSAGE section of the labeling includes cardiac arrest, cardiac arrhythmia, hyperkalemia, hyperphosphatemia, (b) (4) DPV-I recommends the addition of the following terms to the OVERDOSAGE section of the labeling based on our case series: bradycardia and hypotension.

Our case series supports the addition of a warning for risk of cardiac arrest or death associated with bolus/rapid IV administration of potassium phosphates. The applicant's current proposed labeling (b) (4) Of six cases in our case series that described rapid IV administration of potassium phosphates, four experienced cardiac arrest, and two had an outcome of death; five involved rapid "IV push" administration of potassium phosphates injection, including two cases of accidental administration due to confusion of potassium phosphates injection with a heparin flush. In four cases, undiluted potassium phosphates injection was present in a patient care area or at the patient's bedside.

Our case series supports the addition of a warning for risk of cardiac arrest or death associated with IV administration of precipitated calcium/potassium phosphates admixture. The applicant's proposed DRUG INTERACTIONS section of the labeling (b) (4) Of the four cases in our case series that involved IV administration of precipitated calcium/potassium phosphates admixture, three had an outcome of death. These cases involved concomitant administration in the same IV bag of physically incompatible concentrations (i.e., precipitation) of calcium- and phosphate-containing products.

The serious outcomes associated with adverse events in our case series, including deaths, support re-ordering the proposed WARNINGS AND PRECAUTIONS section. The CDER labeling guidance states that "the order in which adverse reactions are presented in the WARNINGS AND PRECAUTIONS section should reflect the relative clinical significance of the adverse reactions. Factors to consider include the relative seriousness of the adverse reaction, the ability to prevent or mitigate the adverse reaction, and the likelihood of its occurrence." Based on our case series, we suggest the following order for the WARNINGS AND PRECAUTIONS section of the potassium phosphates injection labeling: need for dilution/administration at an appropriate rate (5.1), pulmonary embolism due to pulmonary vascular precipitates (5.2), hyperkalemia (5.3), hyperphosphatemia (5.4). Our cases do not contain information to inform the order of the other warnings that the applicant included in WARNINGS AND PRECAUTIONS.

5 RECOMMENDATIONS

We provide recommendations that pertain to the WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, and OVERDOSAGE sections of the applicant's proposed potassium phosphates injection labeling from July 18, 2019.

Our recommendations pertaining to WARNINGS AND PRECAUTIONS are listed below:

- We recommend the addition of a new warning (5.1) to communicate that undiluted potassium phosphates injection should never be directly administered IV, and rapid IV administration of potassium phosphates has been associated with cardiac arrest and death.
- We recommend the addition of a new warning (5.2) to communicate the risk of pulmonary embolism, cardiac arrest, or death due to pulmonary vascular precipitates with IV administration of potassium phosphates.
    - We suggest the following wording for the first sentence of (5.2): Pulmonary vascular precipitates causing pulmonary vascular emboli or respiratory distress have been reported in patients receiving parenteral nutrition or admixed products containing calcium and phosphates.
- We suggest listing the following warnings first and in this order within the WARNINGS AND PRECAUTIONS section of the potassium phosphates injection labeling: need for dilution/administration at an appropriate rate (5.1), pulmonary embolism due to pulmonary vascular precipitates (5.2), hyperkalemia (5.3), hyperphosphatemia (5.4).

Our recommendations pertaining to ADVERSE REACTIONS are listed below:

- (b) (4)
- We recommend the addition of the following wording to reflect that events listed in ADVERSE REACTIONS came from literature *or* postmarketing reports: "The following adverse reactions associated with the use of potassium phosphates injection were identified in the literature or postmarketing reports."
- We recommend the addition of "acute phosphate nephropathy" to the portion of the ADVERSE REACTIONS section specific to IV phosphate administration.
- We recommend the addition of the following terms to the portion of ADVERSE REACTIONS that describes adverse events with combined potassium and phosphate intoxication: bradycardia and cardiac arrest.

Our recommendations pertaining to OVERDOSAGE are listed below:

- We recommend the addition of the following terms to the OVERDOSAGE section of the labeling: bradycardia and hypotension.

6 REFERENCES

1. Institute for Safe Medication Practices List of High-Alert Medications in Acute Care Settings. Updated on August 23, 2018. Available at: https://www.ismp.org/recommendations/high-alert-medications-acute-list. [Accessed July 10, 2019]

2. Agrawal N, Nair N, McChesney LP, Tuteja S, Suneja M, and Thomas CP. Unrecognized acute phosphate nephropathy in a kidney donor with consequent poor allograft outcome. *Am J Transplant* 2009; 9:1685-9.

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

7.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

7.3 APPENDIX C. FAERS DATABASE LINE LISTING OF ADVERSE EVENTS WITH IV POTASSIUM PHOSPHATES CASE SERIES

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
1	2/19/2018	14549256	1	CA-FRESENIUS KABI-FK201801936	Expedited (15-Day)	1	Male	CAN	DE,LT
2	12/27/2006	6212975	1		Direct	24.38	Male	USA	HO
3	8/19/2009	7098986	1	351063	Expedited (15-Day)	30	Female	USA	OT
4	5/27/2004	4148591	1		Direct	36	Female	USA	DE
5	9/26/2001	3714869	1		Direct	42	Female	USA	LT
6	3/13/2006	6012327	1	06H-008-0305968-00	Expedited (15-Day)	43	Male	AUS	LT
7	5/7/2004	4139567	1		Direct	55	Male	USA	LT
8	6/18/2007	6339307	1		Direct	61	Female	USA	
9	2/21/1996	5696185	1		Direct	71	Male	USA	OT
10	10/5/2001	3720793	1		Direct	72	Male	USA	DE
11	11/3/2003	4031331	1	03H-163-0237933-00	Expedited (15-Day)	81	Male	USA	DE
12	3/1/1999	3218063	1		Direct	Not reported	Null	USA	DE
13	6/30/2015	11232097	1		Direct	Not reported	Null	USA	
14	9/23/2003	4009998	1		Direct	Not reported	Null	USA	
15	3/5/1996	5689111	1		Direct	Not reported	Null	USA	DE

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case can have more than one serious outcome.
Abbreviations: DE=Death, HO=Hospitalization, LT= Life-threatening, DS= Disability, CA= Congenital Anomaly, OT=Other medically significant

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/s/

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09/13/2019 01:36:55 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

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

From: Denise Pica-Branco, Ph.D. Senior Regulatory Health Project Manager
Division of Pediatric and Maternal Health

Subject: Division of Gastroenterology and Inborn Error Products (DGIEP) labeling meeting assistance to the Division of Pediatric and Maternal Health (DPMH) requesting assistance with a Pregnancy and Lactation Labeling Rule label

Applicant: FRESENIUS KABI USA LLC

Drug: Potassium Phosphates

NDA: 212832

DPMH provided labeling recommendations to DGIEP. There are no further comments at this time. This consult is considered closed.

Division Director:	Lynne P. Yao
DPMH Medical TL:	Tamara Johnson
DPMH Reviewer:	Kristie Baisden
DPMH CSO:	Rosemary Addy
DPMH RPM:	Denise Pica-Branco

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/s/

DENISE J PICA-BRANCO
09/04/2019 09:50:38 AM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: August 8, 2019

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Thao Vu, RPM
DGIEP

Subject: QT-IRT Consult to NDA 212832 (SDN 001)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 7/10/2019 regarding the sponsor's rationale and justification to support the safety of the proposed product. The QT-IRT reviewed the following materials:

- Summary of clinical safety (Submission 0001); and
- Proposed label (Submission 0001).

1 QT-IRT's Response

Question from the Division: The sponsor provides rationale and justification to support the safety of the proposed product and a waiver of the clinical QTc interval study requirement. Please review and provide comments and your conclusion about the need for further information or studies.

QT-IRT's response: A TQT study is not needed per ICH E14 because the doses for potassium and phosphate are not substantially higher than approved products on US market.

2 Internal Comments to the Division

None.

3 BACKGROUND

3.1 Product Information

Fresenius Kabi USA, LLC is developing Potassium Phosphates Injection, USP, 3 mmol (b) (4) and 4.4 mEq Potassium/mL (170 mg/mL), Sterile Solution for Infusion, in 3 separate presentations (single dose vials of 5 mL, 15 mL and 50 mL). The proposed product 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. The application is submitted as a 505(b)(2) NDA relying on 2 reference listed products to support safety and efficacy, 1) Sodium Phosphates Injection, USP (NDA 018892; Hospira, Inc., 1983), 2) Potassium Chloride Injection (NDA 020161; Hospira, Inc., 1992), and additional literatures to support approval.

The proposed therapeutic dosing is individualized in terms of the (b) (4). The following dosage regimen is proposed by the sponsor based on (b) (4)

(b) (4)

No pharmacokinetic or clinical studies have been performed with the proposed product.

Reviewer's comments:

Phosphate content in the proposed product is the same as the reference product (NDA 18892, 3 mmol Phosphate/mL). (b) (4)

The proposed product will not be administered in patients with serum potassium level >4 mmol/L to prevent hyperkalemia. The proposed label states that serum potassium, (b) (4) *phosphorus and calcium levels should be monitored as a guide to dosage.*

3.2 Sponsor's position related to the question

Not applicable. The sponsor did not submit a request to waive a dedicated QT study.

3.3 Nonclinical Cardiac Safety

Not available. No preclinical studies performed.

3.4 Clinical Cardiac Safety

Not available. No clinical studies have been performed.

3.5 Summary results of prior QTc assessments

Not available. No clinical studies have been performed.

3.6 Relevant details of planned Phase 3 study

Not applicable.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

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08/08/2019 01:09:56 PM
Xiaohui Li is the primary clinical pharmacology reviewer.

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