CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212832Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multidisciplinary Review and Evaluation

Application type	NDA
Application number(s)	212832
Priority or standard	Priority
Submit date(s)	5/29/19
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PDUFA goal date	11/29/19
Division/office	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Review completion date	November 26, 2019
Established/proper name	Potassium Phosphates Injection, USP
(Proposed) trade name	None
Pharmacologic class	Parenteral Phosphorus Replacement
Applicant	Fresenius Kabi USA, LLC
Dosage form	**Injection** • Phosphorus 15 mmol/5 mL (3 mmol/mL) and potassium 22 mEq/5 mL (4.4 mEq/mL) in a single-dose vial. • Phosphorus 45 mmol/15 mL (3 mmol/mL) and potassium 66 mEq/15 mL (4.4 mEq/mL) in a single-dose vial. • Phosphorus 150 mmol/50 mL (3 mmol/mL) and potassium 220 mEq/50 mL (4.4 mEq/mL) in Pharmacy Bulk Package vial.
Applicant-proposed dosing regimen	(b) (4) [redacted] **For Use in Parenteral Nutrition** In patients on total parenteral nutrition, approximately 12 to 15 millimoles of phosphorus (equivalent to 372 to 465 mg elemental phosphorus) per liter bottle of total parenteral nutrition (TPN) solution containing 250 g dextrose is usually adequate to maintain normal serum phosphorus, though larger amounts may be required in hypermetabolic states. The amount of potassium and phosphorus which accompanies the addition of potassium phosphate also should be kept in mind, and if necessary, serum potassium levels should be monitored.
Applicant-proposed indication(s)/population(s)	Potassium Phosphates Injection, USP is indicated as a source of phosphorus, for addition to large volume intravenous fluids, to prevent or correct hypophosphatemia in patients with restricted or no oral intake. It is also useful as an additive for preparing specific parenteral fluid formulas when the needs of the patient cannot be met by standard electrolyte or nutrient solutions.

Recommendation on regulatory action	Approval as a source of phosphorus for correction of hypophosphatemia in intravenous fluids and in parenteral nutrition
Recommended indication(s)/population(s) (if applicable)	Potassium Phosphates Injection, USP is indicated as a source of phosphorus: • in intravenous fluids to correct hypophosphatemia in adults and pediatric patients when oral or enteral replacement is not possible, insufficient or contraindicated • for parenteral nutrition in adults and pediatric patients when oral or enteral nutrition is not possible, insufficient or contraindicated
Recommended dosing regimen	Dosing for both indications can be found in Section 11, Labeling

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OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
EA = Environmental Analysis
DPMH = Division of Pediatric and Maternal Health
DPV = Division of Pharmacovigilance
OPT = Office of Pediatric Therapeutics
QT/IRT = QT Interdisciplinary Review Team

Glossary

AE	adverse event
AET	analytical evaluation threshold
AR	adverse reaction
ASPEN	American Society for Parenteral and Enteral Nutrition
ATP	adenosine triphosphate
BLA	biologics license application
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
DEPI	Division of Epidemiology
DKA	diabetic ketoacidosis
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatric and Maternal Health
DPV	Division of Pharmacovigilance
ECG	electrocardiogram
ESRD	end-stage renal disease
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
ICH	International Council for Harmonisation
ICU	intensive care unit
IND	investigational new drug
IOM	Institute of Medicine
iPSP	initial pediatric study plan
LD	listed drug
MDD	maximum daily dose
mEq	milliequivalents
mmol	millimoles
NDA	new drug application
NF	National Formulary
P	phosphorus
PI	prescribing information
PMC	postmarketing commitment
PN	parenteral nutrition
PO_4	phosphate
QT	time from the start of the Q wave to the end of the T wave in electrocardiogram
RDA	recommended dietary allowance
RDI	reference daily intake
TPN	total parenteral nutrition
USP	United States Pharmacopeia

1. Executive Summary

1.1. Product Introduction

Potassium Phosphates Injection, USP is a phosphorus replacement product containing phosphorus 3 mmol/mL and potassium 4.4 mEq/mL. It is a sterile, nonpyrogenic, concentrated solution containing a mixture of monobasic potassium phosphate and dibasic potassium phosphate in water for injection. It is administered, after dilution or admixing, by intravenous route for phosphorus replacement. The Applicant, Fresenius Kabi USA, LLC, has submitted the new drug application (NDA) for Potassium Phosphates Injection, USP in three separate presentations: 5 mL and 15 mL single-dose vials and 50-mL Pharmacy Bulk Package vial.

The Applicant is not proposing a proprietary name. The Established Pharmacologic Class will be "parenteral phosphorus replacement." The nonproprietary name is Potassium Phosphates Injection, USP.

Each mL contains 224 mg of monobasic potassium phosphate, National Formula (NF) grade, monohydrate, and 236 mg of dibasic potassium phosphate, USP.

The Applicant-proposed indications were:

> *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 solutions.*

The indications recommended for approval are:

- Potassium Phosphates Injection is indicated as a source of phosphorus:
  - In intravenous fluids to correct hypophosphatemia in adults and pediatric patients when oral or enteral replacement is not possible, insufficient, or contraindicated
  - For parenteral nutrition in adults and pediatric patients when oral or enteral nutrition is not possible, insufficient, or contraindicated

The Applicant submitted a 505(b)(2) application based on published literature and two listed drugs (LD):

1. Sodium Phosphates Injection, 45 mmol phosphorus (3 mmol/mL) distributed by Hospira, Inc. (NDA 018892) to support the efficacy and safety of the phosphorus active moiety

   Initial approval for Sodium Phosphates Injection was granted on May 10, 1983. The LD 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 indicated "as an additive for preparing specific parenteral fluid formulas when the needs of the patient cannot be met by standard electrolyte or nutrient solutions."

Monobasic and dibasic sodium phosphate, found in Sodium Phosphates Injection, USP, and monobasic and dibasic potassium phosphate, found in the proposed Potassium Phosphates Injection, USP, are different active ingredients (salts); however, the active moiety, phosphate(s), is the same. Both products provide repletion of phosphorus for correction of hypophosphatemia by the same mechanism of action.

2. Potassium Chloride Injection (NDA 020161; Hospira, Inc., 1992)

   Potassium Chloride Injection supports the safety of the potassium salt in the proposed Potassium Phosphates Injection, USP product.

   In the past, both sodium and potassium phosphates injection products have been on national drug shortage.

   Another Potassium Phosphates Injection, USP product (NDA 212121) was approved on September 19, 2019, for the same indication(s) as the proposed product. The product is supplied as phosphorus 3 mmol/mL and potassium 4.7 mEq/mL in a 15 mL single-dose vial. Due to the aluminum content of the previously approved product (NDA 212121), the indications are limited to pediatric patients 12 years of age and older, as shown below.

   In Intravenous Fluids to Correct Hypophosphatemia

   Potassium Phosphates Injection is 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

   Potassium Phosphates Injection is indicated as a source of phosphorus for parenteral nutrition (PN) 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 PN 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 [see Warnings and Precautions (5.5), Use in Specific Population (8.4)].

There are also several unapproved oral and injectable potassium phosphates products on the market. Sodium phosphates is also used as a cathartic and is found in bowel preps, enema solutions, and other laxatives.

The concentration of phosphate in the proposed to-be-marketed Potassium Phosphates Injection, USP product is the same as in the approved product (NDA 212121) and two of the marketed unapproved potassium phosphates injection products. The concentration of potassium in the proposed product is slightly lower at (4.4 mEq/mL) compared to the approved product (4.7 mEq/mL) and same as the marketed unapproved products (4.4 mEq/mL).

Dosing of Potassium Phosphates Injection, USP is dependent on the indication, see Section 11 for a complete discussion of dosing.

1.2. Conclusions on Substantial Evidence of Effectiveness

The Applicant has requested two indications: (1) to correct hypophosphatemia and (2) as a source of phosphorus in PN.

NDA 212832 relies on Food and Drug Administration's (FDA's) previous findings of safety and effectiveness for the LD, Sodium Phosphates Injection, USP by Hospira, which is indicated for all age groups for both indications. However, dosing recommendations for the LD are not provided for the indication of correction of hypophosphatemia in any age group. Dosing recommendations in PN are provided in the LD's labeling for adults (characterized per Liter of PN containing 250 g dextrose) and infants (characterized per kg), but not for other pediatric age groups.

Therefore, to support dosing regimens for both indications, NDA 212832 also relies on published clinical efficacy studies, primarily in adults, clinical guidelines, oral dietary requirements, postmarketing information, and clinical experience.

Correction of Hypophosphatemia

There are no controlled clinical studies of potassium phosphates in pediatric patients for correction of hypophosphatemia in the published literature. Dosing for pediatric patients is derived from adult data that identified a dosing algorithm, given the similar phosphorus requirements and understanding of the physiology of phosphorus repletion. The recommended dose range for correction of hypophosphatemia is the same in patients of all ages, although the lower end of the reference range for normal serum phosphorus levels is higher in pediatric patients (b) (4). Therefore, the definition of hypophosphatemia, and hence, the threshold for correction, is different.

Additionally, the safety of the potassium salt is supported by the published literature of other intravenous potassium-containing products and the clinical guidelines based on this published literature. The review team agrees with the Applicant's proposed dosing regimen of three dose levels depending on the patients' serum phosphorus level at baseline. However, the review team does not agree with a dose (b) (4) in patients with severe hypophosphatemia, based upon literature that reports serious adverse reactions (ARs) including serious and life-threatening cardiac ARs, with administration of higher single doses or rapid infusion. Therefore, the highest recommended dose initial or single dose is 0.64 mmol/kg (maximum of 45 mmol). Additional dose(s) following the initial dose may be needed in some patients. Prior to administration of additional doses, the patient should be assessed clinically, serum phosphorus, calcium, and potassium concentrations obtained, and the subsequent dose adjusted accordingly.

Use in PN

The Applicant had proposed a recommended dosage of phosphorus of 12 to 15 mmol per liter of PN solution containing 250 g dextrose, consistent with the LD. The review team has proposed a generally recommended phosphorus dosage in adults and pediatric patients independent of

the volume and (caloric) content of the PN solution, that approximates American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines. The dose in pediatric patients 12 years of age and older is recommended to be the same as that in adults (i.e., 20 to 40 mmol/day).

The dose in pediatric patients from birth to less than 12 years of age is supported by various sources, including daily oral requirements, clinical guidelines, and clinical studies. Collectively, these data support a relatively higher daily dosage in pediatric patients from birth to less than 1 year of age (2 mmol/kg), compared to older pediatric patients 1 year of age to less than 12 years of age (1 mmol/kg up to a maximum of 40 mmol).

Overall Conclusion

The Applicant has provided acceptable compatibility/stability studies with normal saline (NS) and 5% dextrose in water (D5W), as well as admixture studies for mixing in PN solutions. The Applicant has not yet submitted the final assay results for PN studies, and these will need to be submitted as a postmarketing commitment (see Section 13). The Applicant commits to submit these assay studies by December 31, 2019. All inspections have been performed and the drug substance and drug product are acceptable to the Chemistry, Manufacturing and Controls reviewers. This application is recommended for approval.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Potassium Phosphates Injection, USP, is proposed as a source of phosphorus for the following two indications:

- 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.

The regulatory recommendation is approval.

Phosphorus is an essential mineral in the body and has a variety of biochemical functions in all organs and tissues of the body. Hypophosphatemia is an expected, and often common, complication of medical treatment, such as treatment of patients with refeeding syndrome, alcoholic patients, or patients with diabetic ketoacidosis. Potassium is also depleted in these conditions. Hypophosphatemia is especially seen in severely ill patients and can be life-threatening. Oral phosphorus replacement is generally administered if hypophosphatemia is mild or moderate in severity, unless the patient is unable to tolerate oral feedings or medications. Severe hypophosphatemia must be corrected intravenously. Therefore, intravenous administration of potassium phosphates can be life-saving and has a long history of clinical use. Potassium phosphates are also added to maintenance intravenous fluids, including PN, to prevent hypophosphatemia (i.e., maintain serum phosphorus concentrations in the normal reference range).

Current FDA-approved treatment options include Sodium Phosphates Injection, USP and another injectable potassium phosphates injectable product (NDA 212121). There are also two unapproved injectable potassium phosphates products on the market, which have been in clinical use for many years. Sodium Phosphates Injection, USP and the marketed, unapproved potassium phosphates products have been on the national drug shortage list in the past. Approval of potassium phosphates injectable products will ensure product quality and availability.

NDA 212832 relies on FDA's previous findings of safety and effectiveness for the Listed Drug (LD), Sodium Phosphates Injection, USP, which is indicated for all age groups as a source of phosphorus for correction of hypophosphatemia and in PN. To support dosing regimens for both indications, NDA 212832 also relies on published clinical efficacy studies, primarily in adults, clinical guidelines, oral dietary requirements, postmarketing, and clinical experience. No clinical studies were conducted by the Applicant.

For the correction of hypophosphatemia, the available clinical data support the recommended dosage range in adults. There are limited data in pediatric patients. However, there appears to be no fundamental difference between adult and pediatric patients in the manifestations of hypophosphatemia or the physiology of phosphorus repletion. Therefore, the recommended dosage regimen is proposed for all ages.

However, adults and pediatric patients less than 1 year of age have different cut-off values for the lower end of the reference range for normal serum phosphorus, which defines hypophosphatemia and the need for correction.

There are limited clinical studies for the use in PN in adults or pediatrics, but the information available aligns with the oral dietary requirements and clinical practice guidelines. Daily dosage recommendations for phosphorus are the same for adults and pediatric patients 12 years of age and older. For younger pediatric patients, the recommended dosing is weight-based. A relatively higher dosage is recommended in pediatric patients from birth (including preterm and term infants) to 1 year of age in order to meet dietary needs.

For both indications, the dosage should be individualized based upon the patient's needs and must take both baseline potassium and phosphorus concentrations into consideration. Close monitoring of serum phosphorus, potassium, calcium, and magnesium concentrations are recommended to guide dosing and monitor safety before, during, and after administration.

The safety profile of the product is characterized both by the active moiety (phosphorus) and the salt (potassium). Serious adverse reactions associated with intravenous administration include hyperphosphatemia, hyperkalemia, hypocalcemia, and hypomagnesemia. These adverse reactions are primarily reported with higher than recommended dosages, inadequate dilution, and/or rapid infusion. The known risks can be mitigated with proper patient selection, preparation, administration, dosing, and monitoring per the labeling. When prepared and administered as recommended, adverse reactions are rarely clinically significant. No new safety signals are expected postmarketing.

In summary, Potassium Phosphates Injection, USP represents a medically necessary product, meeting quality and control standards, as a source of phosphorus to correct hypophosphatemia and for use in PN in adult and pediatric patients when oral or enteral replacement/nutrition is not possible, insufficient, or contraindicated. Recommendations for dosing are supported by clinical data and align with treatment guidelines. The safety profile is well characterized. Known risks can be mitigated with proper patient selection, preparation, administration dosing, and monitoring as per labeling. Therefore, the overall benefit-risk assessment for Potassium Phosphates Injection, USP is favorable and the drug is recommended for approval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Phosphorus is one of the most abundant mineral elements in the human body. Most phosphorus in the body is complexed with oxygen (O_2) as phosphate (PO_4^{-3}). • Phosphorus is primarily an intracellular anion, which makes an estimation of total body phosphorus levels clinically unfeasible. However, serum levels are reflective of phosphorus available for energy production, and low serum phosphorus levels are associated with adverse clinical outcomes. • Phosphorus in the form of organic and inorganic phosphate has a variety of biochemical functions in all organs and tissues, including critical roles in nucleic acid structure, energy storage and transfer, cell signaling, cell membrane composition and structure, acid-base balance, mineral homeostasis, and bone mineralization. • Hypophosphatemia is common in hospitalized and especially prevalent in severely ill patients, with reports of frequencies as high as 30-40%, and can be life-threatening. • Clinical features of hypophosphatemia include muscle weakness, rhabdomyolysis, hemolysis, respiratory failure and heart failure, seizures, and coma. • Mild and moderate hypophosphatemia is generally corrected with oral replacement products, unless the patient is unable to tolerate oral feedings or medications. Severe hypophosphatemia should be corrected intravenously.	• Infusion of potassium phosphate products can be life-saving for patients in whom oral or enteral administration is not possible, insufficient, or contraindicated.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• There are two marketed unapproved injectable potassium phosphate products that have been in clinical use for many years and have frequently been on the national drug shortage list. • There are two approved products: Sodium Phosphates Injection, USP (NDA 18892; approved 1983) and another potassium phosphates injection product (NDA 212121; approved 2019). • The recently approved potassium phosphates injection product is only approved in adults and pediatric patients 12 years of age and older, due to the aluminum content of the product. • Sodium Phosphates Injection, USP has also been on the national drug shortage list, in the past. • The choice of sodium or potassium salt for phosphorus replacement/supplementation depends on the individual patient's electrolyte status. Sodium is associated with complications of fluid overload and potassium can result in cardiac complications due to hyperkalemia.	• Both potassium and sodium phosphates injection products are critical to public supply and patient needs. • Approved injectable potassium phosphates products provide assurance of product quality and availability.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Potassium Phosphates Injection, USP demonstrated acceptable quality and manufacturing controls. • Compared to the other approved potassium phosphates injectable product (NDA 212121), the Applicant's maximum aluminum content/specification is acceptable, and the aluminum exposure does not exceed 5 mcg/kg/day for the indicated population per 21 CFR 201.323; therefore, Potassium Phosphates Injection, USP is safe for pediatric patients of all ages (birth to <18 years) and adults. • NDA 212832 relies on FDA's previous findings of safety and effectiveness for the LD, Sodium Phosphates Injection, USP, which is indicated for all age groups for the correction of hypophosphatemia and use of phosphorus in PN. • To support dosing regimens for both indications, NDA 212832 also relies on published clinical efficacy studies, primarily in adults, clinical guidelines, oral dietary requirements, postmarketing, and the long-standing clinical experience and guidelines based on the published literature. No clinical studies were conducted by the Applicant. • For the correction of hypophosphatemia, the available clinical data support the recommended dosage range in adults. There is limited data in pediatric patients. However, there appears to be no fundamental difference between adult and pediatric patients in the manifestations of hypophosphatemia or the physiology of phosphorus repletion. • For the use in PN, there are limited clinical studies in adults or pediatrics, but the informational available aligns with the oral dietary requirements and clinical practice guidelines.	• For the correction of hypophosphatemia, the recommended dosage regimen is proposed for all ages. However, adults and pediatric patients less than 1 year of age have different cut-off values for the lower end of the reference range for normal serum phosphorus, which defines hypophosphatemia and the need for correction. • Daily dosage recommendations for phosphorus in PN are the same for adults and pediatric patients 12 years of age and older. For younger pediatric patients, the recommended dosing is weight-based. A relatively higher dosage is recommended in pediatric patients from birth (including preterm and term infants) to 1 year of age in order to meet dietary needs. • For both indications, the dosage should be individualized based upon the patient's needs. Monitoring of serum phosphorus, potassium, calcium, and magnesium concentrations is recommended to guide dosing and monitor safety.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The safety profile of the product is characterized both by the active moiety (phosphorus) and the salt (potassium) and includes issues such as hyperkalemia, hyperphosphatemia, hypocalcemia, hypomagnesemia, and systemic calcium precipitation. • Serious adverse reactions, including cardiac, associated with intravenous administration are primarily reported with higher-than-recommended dosages, inadequate dilution, and/or rapid infusion. • When prepared and administered as recommended, adverse reactions are rarely clinically significant. • No new safety concerns are expected in the postmarket setting with this potassium phosphate product. • The Applicant has performed compatibility/stability and admixture studies with normal saline solution, 5% dextrose in water (D5W), Clinimix-E and Kabiven in which appearance, pH, and particulate matter were assessed without evidence of precipitates of phosphate salts in the admixed solutions supporting compatibility with these diluents and PN solutions.	• Dosing of Potassium Phosphates Injection, USP must take both potassium and phosphate concentrations in patients into consideration. • To minimize the risks, Potassium Phosphates Injection, USP is contraindicated in patients with hyperkalemia; hyperphosphatemia; hypercalcemia or significant hypocalcemia; or severe renal impairment (eGFR less than 30 mL/min/1.73 m^2) or end-stage renal disease. • Patients with moderate renal impairment should receive the lower end of the recommended dosage range. • When administering Potassium Phosphates injection, USP for the correction of hypophosphatemia, the baseline serum potassium level should be assessed, and the drug should not be administered to patients with serum potassium levels <4 mEq/dL. • Maximum concentration and infusion rates for administration through a peripheral and central venous catheter will be provided in labeling. • The known risks can be mitigated with proper patient selection, preparation, administration dosing, and monitoring as per the labeling. • Routine pharmacovigilance is recommended. • There are no recommendations for risk management (risk evaluation and mitigation strategies or Food and Drug Administration Amendments Act of 2007 postmarket requirements) beyond labeling recommendations. • Assay results for the PN admixture study are pending at the time of approval, but are not considered necessary for the safety assessment. The Applicant will be issued a postmarketing commitment (PMC) and can submit the results postapproval.

1.4. Patient Experience Data

Patient Experience Data Relevant to This Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient-reported outcome (PRO)	
		☐	Observer-reported outcome (ObsRO)	
		☐	Clinician-reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application.**			

2. Therapeutic Context

2.1. Analysis of Condition

2.1.1. Phosphorus

Phosphorus is one of the most abundant elements in the human body. Most phosphorus in the body is complexed with O_2 as phosphate (PO_4^{-3}). Approximately 85% of the about 500 to 700 g of phosphate in the body is contained in bone (Lentz et al. 1978; Bringhurst et al. 2015; Lewis 2018), where it is an important constituent of crystalline hydroxyapatite. In soft tissues, phosphate is mainly found in the intracellular compartment as an integral component of several organic compounds, including nucleic acids and cell membrane phospholipids. Phosphate is also involved in aerobic and anaerobic energy metabolism. Phosphorus, present in large amounts in erythrocytes and other tissue cells, plays a significant intracellular role in the synthesis of high-energy organic phosphates.

Phosphorus has been shown to be essential to maintain red cell glucose utilization, lactate production, and the concentration of both erythrocyte adenosine triphosphate (ATP) and 2,3 diphosphoglycerate, which play crucial roles in O_2 delivery to tissue. Adenosine diphosphate and ATP contain phosphate and utilize the chemical bonds between phosphate groups to store energy (Blaine et al. 2015). Inorganic phosphate is a major intracellular anion but is also present in plasma. The normal serum inorganic phosphate concentration in adults ranges from 2.5 to 4.5 mg/dL (0.81 to 1.45 mmol/L) (Bringhurst et al. 2015). Phosphate concentration is 50% higher in infants and 30% higher in children compared to that in adults, possibly because of the important roles these phosphate-dependent processes play in growth (Lewis 2018).

Maintaining normal phosphorus concentrations is essential for optimal cellular function. The kidney and (to a lesser extent) the small intestine are the main organs that maintain phosphorus homeostasis. A large proportion of dietary phosphate is absorbed from the gastrointestinal tract and excreted in urine. In proximal tubule cells and enterocytes, type II sodium-phosphate cotransporters (NaPi-II) are expressed in the apical membrane; their activity rate limits transepithelial phosphate transport. NaPi-II expression in both cell types is controlled by hormones and metabolic factors in response to homeostatic needs (Lewis 2018). Two hormones play important roles in renal phosphate handling: parathyroid hormone and fibroblast growth factor 23 (FGF-23) (Bacchetta and Salusky 2012; Blaine et al. 2015; Bringhurst et al. 2015). Both hormones have hypophosphatemic effects by decreasing the tubular reabsorption of phosphate. Another main regulator of phosphate metabolism is 1,25-dihydroxy vitamin D, which increases intestinal absorption of phosphate and inhibits parathyroid hormone synthesis (Bacchetta and Salusky 2012; Blaine et al. 2015; Bringhurst et al. 2015). Similar to calcium, gastrointestinal phosphate absorption is enhanced by vitamin D. Renal phosphate excretion roughly equals gastrointestinal (GI) absorption to maintain phosphate balance. Phosphate depletion can occur in various disorders and normally results in conservation of phosphate by the kidneys. Bone phosphate serves as a reservoir, which can buffer changes in plasma and intracellular phosphate.

2.1.2. Hypophosphatemia

Hypophosphatemia can be caused by three different mechanisms: decreased intestinal absorption, increased renal excretion, or internal redistribution of inorganic phosphate. Most information comes from an understanding of physiology; i.e., requirement of phosphorus for known vital functions of body (ADP/ATP in erythrocytes for carrying oxygen and delivering oxygen to various tissues), bone health, etc. Additional information is available from studies that correlate poor patient outcomes to low phosphorus levels.

Hypophosphatemia has numerous causes (Bringhurst et al. 2015), but clinically significant acute hypophosphatemia occurs in relatively few clinical settings (Lentz et al. 1978), including the following:

- Recovery phase of diabetic ketoacidosis
- Acute alcoholism
- Severe burns
- During PN
- Refeeding after prolonged malnutrition
- Severe respiratory alkalosis

Chronic hypophosphatemia is usually the result of decreased renal phosphate reabsorption, which can be caused by the following:

- Hyperparathyroidism
- Other hormonal disturbances, such as Cushing syndrome and hypothyroidism
- Electrolyte disorders, such as hypomagnesemia and hypokalemia
- Theophylline intoxication
- Long-term diuretic use

Severe chronic hypophosphatemia usually results from a prolonged negative phosphate balance secondary to:

- Chronic starvation or malabsorption, especially when combined with vomiting or copious diarrhea
- Long-term ingestion of aluminum, such as in some antacids, is particularly prone to cause phosphate depletion when combined with decreased dietary intake and dialysis losses of phosphate in patients with end-stage renal disease. It is important to note that aluminum-containing antacids are no longer commonly used in clinical practice.

Clinical features of hypophosphatemia include muscle weakness, rhabdomyolysis, hemolysis, respiratory failure, and heart failure; seizures and coma can also occur (Lentz et al. 1978; Bringhurst et al. 2015; Medscape 2018). The diagnosis is determined by serum phosphate concentration, and treatment consists of phosphate supplementation via oral or intravenous administration.

In adults, hypophosphatemia, especially severe hypophosphatemia, is more common in severely ill patients in the intensive care unit (ICU). Although the incidence of hypophosphatemia in the general hospital population is 0.5% to 3%, several reports have shown that patients receiving specialized nutrition support have a frequency of hypophosphatemia of 30% to 40% (Gilbert et al. 1970; Ruberg et al. 1971; Betro and Pain 1972; Freiman et al. 1982; Weinsier et al. 1982; Larsson et al. 1983; Thompson and Hodges 1984; Sacks et al. 1994; Waterlow and Golden 1994). Urgent treatment of hypophosphatemia is generally required only in patients with serum phosphorus levels less than 1 mg/dL.

The serum phosphorus concentration in adults ranges between 2.5 and 4.5 mg/dL. Net intestinal phosphate absorption from diet generally ranges between 500 and 1000 mg/day (16 to 32 mmol/day). Acute severe hypophosphatemia with serum phosphorus concentration of <1 mg/dL is most often caused by transcellular shifts of phosphate, often superimposed on chronic phosphate depletion. In general, patients with serum phosphate levels <1 mg/dL should be treated in an ICU with continuous cardiac monitoring during central venous catheter infusion of phosphorus (Bringhurst et al. 2018).

In pediatric patients, hypophosphatemia (also generally defined as serum phosphorus concentration of <1 mg/dL) is also found in severely ill patients in the pediatric or neonatal ICU.

The prevalence of hypophosphatemia, as well as complications associated with hypophosphatemia, have been described in three clinical trials (Freiman et al. 1982; Waterlow and Golden 1994; Manary et al. 1998) in malnourished children in the outpatient setting, of which one is described below. Similar findings were described in the remaining two studies.

(Manary et al. 1998) described the prevalence of hypophosphatemia in a prospective study of malnourished (subtype - kwashiorkor) children. Children <10 years of age were enrolled during a 2-month period and were supplemented with enteral nutrition, with either egg white (n=37) or milk (n=31) as source of nutrition and protein. Children in both groups had hypophosphatemia; however, the case fatality rate was 63% (5/8 children) in children with serum phosphate <0.32 mmol/L (0.99 mg/dL); 23% (10/44 children) in children with serum phosphate between 0.33 to 0.96 mmol/L (1 to 2.9 mg/dL); and 19% (3/16) in children with serum phosphate >0.96 mmol/L (>2.9 mg/dL). Hypophosphatemia was defined as serum phosphorus 2.9 mg/dL or 0.96 mmol/L; severe hypophosphatemia was defined as serum phosphorus <0.99 mg/dL. Overall, 43% of children had serum phosphorus <0.96 mmol/L (<2.9 mg/dL) and 12% presented with severe hypophosphatemia. The authors concluded that severe hypophosphatemia at any time during the first 48 hours of treatment was associated with death. This study suggests that children who are malnourished may have phosphorus depletion instead of the intracellular shift that can occur due to respiratory alkalosis, and that severe hypophosphatemia is associated with poor outcomes, including death.

Three articles about the frequency of hypophosphatemia in acutely or critically ill children and one article in very low birth weight infants were reviewed (Antachopoulos et al. 2002; Menezes et al. 2006; Santana e Meneses et al. 2009; Kilic et al. 2012; Ross et al. 2013; Rady et al. 2014). The presence of hypophosphatemia in the three publications with critically ill children was

defined by the authors according to age: <3.8 mg/dL for ages 1 month to 3 years, <3.7 mg/dL for ages 3 to 11 years, <2.9 mg/dL for ages 11 to 12 years, and <2.7 mg/dL for ages 15 to 19 years. Hypophosphatemia was defined as serum phosphate value <1.30 mmol/L (4 mg/dL) for patients <1 year including preterm infants.

The three studies summarized below (Menezes et al. 2006; Santana e Meneses et al. 2009; Rady et al. 2014) demonstrate that significant numbers of children admitted to the pediatric intensive care unit were noted to have hypophosphatemia. This suggests that critically ill children may need hypophosphatemia correction. Other published articles support the same finding; i.e., hypophosphatemia in critically ill children is a common finding. One difficulty in interpreting these studies is lack of a uniform definition for hypophosphatemia. Another missing piece of information is whether the children in these studies also received phosphate replacement enterally and/or intravenously for correction of hypophosphatemia. These articles also do not provide information on dose and rate of phosphate infusion.

Table 1. Prevalence of Hypophosphatemia in Pediatric Patients

Reference	Design/Drug	Population	Doses	Outcomes	Key Findings	Complications	Comments
Menezes et al. (2006)	Retrospective review; age 5 months ±4.5 months	Critically ill children (n=42) admitted to PICU	N/A	Serum P was measured on Day 3 of admission	76% of children were found to have hypoP defined as P<3.8 mg/dL; malnourished children had a higher incidence of hypoP	None related to PO_4 replacement	HypoP is common in children admitted to PICU; malnourished children are particularly at risk of developing hypoP and refeeding syndrome
Santana e Meneses et al. (2009)	Prospective study; age 1.8 (0.43-7.17) years	82 children admitted to PICU; 29% were malnourished at baseline	Enteral nutrition was increased and PN was reduced as the child tolerated enteral feeding	Serum P measured for first 10 days of admission; serum P was <1 mg/dL in 1 patient, between 1.0 and 2.0 mg/dL in 8 patients, and between 2.0 and 3.0 mg/dL in 10 patients	HypoP with serum levels <2.5 mg/dL was found in 31 patients; prevalence of hypoP was 62% (n=50) during the first 10 days of ICU stay	None related to PO_4 replacement	HypoP was more common in malnourished children compared to well-nourished children
Rady et al.(2014)	Retrospective chart review; 15 to 49 months (1 year to 4 years)	72 children admitted to PICU	N/A	Serum P measured on first 7 days of admission	58% of patients were found to have hypoP	Definition of hypoP was serum P<4.8 mg/dL for ages 0 to 5 days, <3.8 mg/dL for ages 1 year to 3 years, and <2.9 mg/dL for ages 12 to 15 years	HypoP was a common problem observed in the ICU and was associated with malnutrition.

Reference	Design/Drug	Population	Doses	Outcomes	Key Findings	Complications	Comments
Ross et al. (2013)	Retrospective study	VLBWI with IUGR (n=271) compared to those without IUGR (n=1982)	P replacement doses were not provided in the article, infants most likely received enteral and parenteral nutrition simultaneously	HypoP was most evident on Day 3 following refeeding and was associated with prolonged mechanical ventilation	IUGR infants were more likely to have hypoP relative to non-IUGR infants, 41% vs. 8.9%; RR (95% CI: 7.25 (5.45, 9.65)) and severe hypoP, 11.4% vs. 1%; RR (95% CI: 12.06 (6.82, 21.33)) in first postnatal week	Refeeding syndrome can occur in VLBWI with IUGR	Definition of hypoP was serum P<4 mg/dL and severe hypoP was defined as P<2.5 mg/dL; hypoP was evident on Day 3

Abbreviations: CI = confidence interval; hypoPO_4 = hypophosphatemia; ICU = intensive care unit; IUGR = intrauterine growth retardation; P = phosphorus; PICU = pediatric intensive care unit; PN = parenteral nutrition; RR = relative risk; VLBWI = very-low-birth-weight infants
Source: Reviewer-generated table summarizing the published literature

Serum Phosphorus Concentrations

While reference labs can vary in their reference ranges, the most commonly reported reference range for serum phosphorus in adults is 2.5 to 4.5 mg/dL.

For children, the reference range is generally higher.

In pediatric males, the reference range is as follows:

- Age 0 to 12 months: Not established
- Age 1 to 4 years: 4.3 to 5.4 mg/dL
- Age 5 to 13 years: 3.7 to 5.4 mg/dL
- Age 14 to 15 years: 3.5 to 5.3 mg/dL
- Age 16 to 17 years: 3.1 to 4.7 mg/dL
- Age 18 years or older: 2.5 to 4.5 mg/dL

In pediatric females, the reference range is as follows:

- Age 0 to 12 months: Not established
- Age 1 to 7 years: 4.3 to 5.4 mg/dL
- Age 8 to 13 years: 4 to 5.2 mg/dL
- Age 14 to 15 years: 3.5 to 4.9 mg/dL
- Age 16 to 17 years: 3.1 to 4.7 mg/dL
- Age 18 years or older: 2.5 to 4.5 mg/dL

The provided literature evidence (see Section 8.1.1) demonstrates that serum levels of phosphorus increased in hypophosphatemic patients who received intravenous potassium phosphates. Since most of the phosphorus in the human body is intracellular, serum levels are not always an accurate reflection of total body phosphorus stores and as such, replacement must be individualized based on daily requirements and the clinical condition of the patient.

2.1.3. Phosphorus Use in Parenteral Nutrition

See Section 8.1.1.

Parenteral nutrition is a vital therapeutic modality for neonates, children, and adults for many indications used in a variety of settings. Appropriate use of this complex therapy maximizes clinical benefit while minimizing the potential risk for adverse events (AEs). Total parenteral nutrition (TPN) is one of the nutritional strategies most associated with hypophosphatemia. Phosphorus imbalance usually occurs during the first week of nutritional intervention and may be present from the first day on PN. Previous studies have provided different recommendations regarding phosphorus needs, expressed per total energy (7 to 10 mmol/1000 kcal or 15 to 25 mmol/1000 kcal), per kilogram of body weight (0.5 mmol/kg), per daily amount (20 to 30 mmol/day or 9.9 to 14.8 mmol/day) or per volume of nutritive solution (6.2 mmol/L or 8.5 to

14.5 mmol/L) (Takala et al. 1985; Greene et al. 1988; Skipper 1998; Prinzivalli and Ceccarelli 1999; Waitzberg 2001; Fernandes et al. 2009).

Dosage and administration information for phosphorus in adults receiving PN is supported by clinical studies (Clark et al. 1995; Brown et al. 2006), guidelines (Greene et al. 1988; Mirtallo et al. 2004; McClave et al. 2016; Mihatsch et al. 2018; American Society for Parenteral and Enteral Nutrition (ASPEN) 2019), and textbooks.

Dosage and administration information for phosphorus in infants and older pediatric patients, receiving PN is also cited in several guidelines (Kahl and Hughes 2017; Taketomo 2017), pediatric textbooks, and publications. The pediatric recommendations appear to derive primarily from adult clinical studies and established practices at various pediatric medical centers.

The recommended daily dietary intake (RDI) and recommended daily allowance (RDA) of oral phosphorus, as well as data from limited clinical studies of neonates receiving PN, suggest that phosphorus requirements of the neonate and infant are higher than those of pediatric patients older than 1 year of age, and that pediatric patients 12 years of age and older have similar requirements to adults (see Section 8.1.1).

2.2. Analysis of Current Treatment Options

Hypophosphatemia is preferably corrected with oral formulations of phosphorus, especially when mild or moderate in severity; however, if the patient is unable to tolerate oral replacements or has severe hypophosphatemia (<1 mg/dL), then an intravenous formulation(s) is used. Phosphorus can also be repleted by rectal instillation of phospho-soda; however, the absorption of phosphorus under these circumstances is unpredictable.

There are two marketed unapproved injectable formulations of potassium phosphates. Potassium phosphates injection, USP (NDA 212121) was approved on September 19, 2019, for adults and adolescents (age ≥12 years). There is also one approved injectable formulation of sodium phosphates on the market (NDA 18892, the LD) (Table 2). Potassium phosphates and sodium phosphates should not be used interchangeably. The choice of salt (sodium or potassium) for phosphorus replacement is dependent on the patients' serum electrolytes and other underlying medical conditions (e.g., renal insufficiency). In the past, injectable phosphate salts have been in shortage.

Table 2. Other Treatment Options for Hypophosphatemia or Use in Parenteral Nutrition

Product Name	Relevant Indication	Year of Approval	Dosing/Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA-Approved Treatments						
Sodium Phosphates Injection, 45 mmol (3 mmol/mL)	Treatment and prevention of hypophosphatemia; additive to PN	1983 (NDA 018892)	Phosphorus 3 mmol/mL; sodium 4 mEq/mL	None provided in labeling; safety and efficacy established for all ages	Hypocalcemia and hypernatremia; hyperphosphatemia possible with overdose or in patients with renal failure or severe adrenal insufficiency	Manufacturer: HOSPIRA, INC.
Potassium Phosphates Injection, USP	Treatment and prevention of hypophosphatemia; additive to PN	2019 (NDA 212121)	Potassium Phosphates Injection, USP, phosphorus 3 mmol/mL and potassium 4.7 mEq/mL	505(b)(2): Relies on LD (Sodium Phosphates Injection, USP) and published literature	Serious cardiac adverse events with undiluted, rapid, bolus IV administration, hyperkalemia, hyperphosphatemia, hypomagnesemia	Manufacturer: CMP Pharma Inc.
Other Marketed Treatments						
Potassium phosphates, injection, solution, concentrate, 224 mg of monobasic and 236 mg of dibasic potassium phosphate	Treatment and prevention of hypophosphatemia; additive to PN	Unapproved	Phosphorus 3 mmol/mL and potassium 4.4 mEq/mL; dose and rate of administration are dependent upon individual needs of patient	None provided in labeling	Hypocalcemia and hyperkalemia; hyperphosphatemia possible with overdose or pts with renal failure or adrenal insufficiency	Manufacturer: HOSPIRA, INC. (141588017)
Potassium Phosphates Injection, solution, concentrate, 224 mg of monobasic and 236 mg of dibasic potassium phosphate	Treatment and prevention of hypophosphatemia; additive to PN	Unapproved	Phosphorus 3 mmol/mL, Potassium 4.4 mEq/mL; dose and rate of administration are dependent on individual needs of patient	None provided in labeling	Hypocalcemia and hyperkalemia; hyperphosphatemia possible with overdose or pts with renal failure or adrenal insufficiency	Manufacturer: Fresenius Kabi

Abbreviations: IV = intravenous; LD = listed drug; mEq = milliequivalents; mmol = millimoles; NDA = new drug application; PN = parenteral nutrition; USP = U.S. Pharmacopeia

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Approved and marketed unapproved products for phosphorus repletion are shown in Table 2 above. In the past, injectable forms of phosphates salts have been in drug shortage. On September 19, 2019, Potassium Phosphates Injection, USP (NDA 212121) was approved by FDA. The Applicant is using the approved Sodium Phosphates Injection, USP, (NDA 18892) as an LD for this 505(b)(2) application, which also relies upon published literature.

3.2. Summary of Presubmission/Submission Regulatory Activity

3.2.1. IND 130166

March 21, 2016

IND 130166 opened.

May 31, 2016

A Type C meeting was held between the Applicant and FDA to obtain FDA's opinion and concurrence that the available literature adequately establishes the safety to support a 505(b)(2) NDA submission for Potassium Phosphates Injection, USP. The Applicant requested concurrence that they do not need to conduct any nonclinical or clinical studies. (b) (4)

FDA agreed no additional studies were required. FDA disagreed (b) (4) and proposed that published literature was needed to support pediatric use and that the Applicant should submit an agreed initial pediatric study plan (iPSP) prior to the NDA.

November 30, 2017

The Applicant submitted an iPSP (submission 0001) and a revised version (submission 0002) on December 5, 2017, (b) (4). FDA disagreed (b) (4) and proposed that a scientific bridge should be provided using published literature, consensus papers, and/or clinical guidelines to support full pediatric dosing.

June 4, 2018

The Applicant submitted revised versions of the iPSP (submissions 0003 and 0004). FDA proposed additional modifications.

September 24, 2018

The Applicant accepted FDA's recommendations and the final agreed iPSP (0005) was submitted.

May 29, 2019

NDA submitted.

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

An Office of Scientific Investigations audit was not requested or performed given that the Applicant did not conduct any clinical trials.

4.2. Product Quality

4.2.1. Drug Substances

The active ingredients in the drug product are monobasic potassium phosphate, NF, and dibasic potassium phosphate, USP. Both ingredients are manufactured by (b) (4) and are controlled to conform to the requirements (specifications) to produce Potassium Phosphates Injection, USP.

Monobasic Potassium Phosphate, NF

This white, granular, or crystalline powder is freely soluble in water and practically insoluble in alcohol. Its melting point is 252.6°C, at which it decomposes. Its molecular formula is $KH2PO_4$ and molecular weight is 136.09. The complete chemistry, manufacturing, and controls (CMC) information regarding raw materials, manufacturing, purification, characterization, stability, storage, and container closure is provided in DMF (b) (4). A Letter of Authorization was also submitted by the manufacturer. The manufacturing process, specification, and stability data of monobasic potassium phosphate were deemed adequate per the drug substance reviewer.

Dibasic Potassium Phosphate, USP

This colorless or white, granular powder is freely soluble in water and very slightly soluble in alcohol. Its melting point is >465°C, at which it decomposes. Its molecular formula is $K2HPO_4$ and its molecular weight is 174.20. The complete CMC information regarding raw materials, manufacturing, purification, characterization, stability, storage, and container closure is provided in DMF (b) (4). A Letter of Authorization was also submitted by the manufacturer. The manufacturing process, specification, and stability data of dibasic potassium phosphate were deemed adequate per the drug substance reviewer.

The biopharmaceutical classification, particle size, and polymorphism of both drug substances are not important because the drug product is an injection for intravenous administration.

4.2.2. Drug Product

Potassium Phosphates Injection, USP, containing phosphorus 3 mmol/mL and potassium 4.4 mEq/mL, is a sterile, nonpyrogenic, aqueous solution of monobasic potassium phosphate and

dibasic potassium phosphate. Each mL of the drug product contains 224 mg of monobasic potassium phosphate and 236 mg dibasic potassium phosphate in water for Injection.

The drug product is supplied as a 5-mL, 15-mL, and 50-mL plastic vial, closed with a grey rubber stopper and sealed with a flip-off cap. The 50 mL drug product is a pharmacy bulk package. The drug product is not for direct intravenous infusion; it must be diluted or added to TPN solution prior to intravenous administration. As there are no preservatives or anti-oxidants in the drug product formulation, it is a single-use drug product and the unused portion should be discarded.

Potassium Phosphates Injection, USP is manufactured by Fresenius Kabi, USA, LLC.; Grand Island, NY by (b) (4) manufacturing process. (b) (4) . The drug product manufacturing process, in-process controls, drug product release tests, and executed batch records were reviewed and deemed satisfactory.

In the Potassium Phosphates Injection, USP admixture compatibility study with 0.9% Sodium Chloride Injection and 5% Dextrose Injection as diluents, the admixtures were stable up to 48 hours at 25°C and up to 14 days at 5°C.

During the Potassium Phosphates Injection, USP admixture compatibility study with TPN (e.g., Clinimix-E from Baxter and Kabiven from Fresenius Kabi), no precipitates of phosphate salts were observed in the admixtures and particulate matter was within specification limits. Thus, the drug product appears to be compatible with TPN, but the Applicant has committed to submitting assay results of the admixture to confirm that strength is not compromised before its administration.

The Applicant provided adequate justification for the differences in the physicochemical properties between the proposed and the LD. The information provided in accordance with 21 Code of Federal Regulations (CFR) 320.24 (b)(6) supporting the relative bioavailability of the proposed drug product to the LD was deemed to be adequate to establish a biobridge to the Agency's finding of safety and efficacy of the LD. Thus, an additional in vivo bioequivalence bridging study is not needed.

The Applicant has provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed Potassium Phosphates Injection, USP: phosphorus 3 mmol/mL and potassium 4.4 mEq/mL.

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

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

The label/labeling is satisfactory from the CMC perspective.

Therefore, from the Office of Pharmaceutical Quality perspective, this NDA is recommended for approval.

4.3. Clinical Microbiology

The (b) (4) container integrity as well as the microbiology related attributes of the drug product specification including bacterial endotoxins, sterility and container closure integrity etc. were reviewed. This NDA is recommended for approval based on drug product sterility assurance from the microbiological perspective.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

From the nonclinical perspective, no approvability issues have been identified for the proposed product at the proposed doses.

No nonclinical studies have been conducted by the Applicant with Potassium Phosphates Injection, USP. The Applicant is relying on FDA's finding of safety for Sodium Phosphates Injection, USP (NDA 018892) and Potassium Chloride Injection (NDA 020161), as well as published literature, to support the safety of their drug product in a 505(b)(2) NDA for Potassium Phosphates Injection, USP. This approach is acceptable. For a discussion of dose acceptability, see Section 8.

The Applicant conducted a risk assessment of all Class 1, 2A, 2B, and 3 elemental impurities recommended in International Council for Harmonisation (ICH) Q3D, as well as (b) (4), based on a maximum dose for Potassium Phosphates Injection, USP of phosphorus 50 mmol/day ((b) (4) mL/day), which is higher than the intended maximum daily dose (MDD) of 45 mmol/day ((b) (4) mL/day) for the treatment of patients with hypophosphatemia. An extractables/leachables assessment for the container closure system was also conducted. There are no safety concerns for elemental impurities or identified leachables from the drug product container closure system.

5.2. Referenced NDAs, BLAs, DMFs

NDA 018892: Sodium Phosphates Injection, USP; approved May 1983

NDA 020161: Potassium Chloride Injection, USP; approved November 1992

5.3. Toxicology

5.3.1. Safety Assessment of Elemental Impurities

The Applicant conducted a risk assessment of all Class 1, 2A, 2B, and 3 elemental impurities recommended in ICH Q3D. A risk assessment was also conducted for (b) (4). The Applicant's specifications for elemental impurities, including (b) (4) are adequate per ICH Q3D.

Table 3. Permitted Daily Exposures and Concentrations of Elemental Impurities

No.	Elements	PDE (ICH Q3D) (µg/day)	Permitted Concentration in Finished Product (µg/mL) [a]	Permitted Concentration in Final Sample Solution (J) (ppb) [b]	0.3J (ppb) [c]	0.3 x Permitted Concentration in Finished Product (ppb) [d]
1						(b) (4)
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						

For Footnotes a, b, c and d: Calculation example using (b) (4) for product:

(b) (4)

Abbreviations: ICH = International Council for Harmonisation; PDE = permitted daily exposure; ppm = parts per million; ppb = parts per billion

5.3.2. Safety Assessment of Aluminum

Per 21 CFR 201.323, the prescribing information (PI) for all large volume parenterals (LVPs), small volume parenterals (SVPs), and pharmacy bulk packages (PBPs) used in TPN must contain a warning statement. This warning must be contained in the "Warnings" section of the labeling. The warning must state: "This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum. Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 µg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration."

The Applicant's aluminum specification of 2000 µg/L is acceptable in adult and pediatric patients. The daily adolescent (>12 years old) and adult patient exposure to aluminum at this specification, based on a recommended daily dose in TPN of 20 to 40 mmol/day, will not exceed 0.67 mcg/kg/day. Daily infant and pediatric patient (b) (4) exposure to aluminum at this specification, based on a MDD in TPN of 2 mmol/kg/day, will not exceed 1.4 mcg/kg/day. As this is a SVP intended for use in a multicomponent PN, this specification and daily exposure limit of aluminum should ensure the daily patient exposure from all potential sources of aluminum in the TPN admixture does not exceed 5 mcg/kg/day (21 CFR 201.323).

Table 4. Daily Aluminum Exposure From Potassium Phosphates Injection, USP (3 mmol/mL)

Patient Population	Recommended Phosphorus Daily Dose	Aluminum Exposure (based on 2000 mcg/L)
Preterm/term infants	2 mmol/kg/day	1.4 mcg/kg/day
(b) (4)		
Pediatric patients 1 year to <12 years old ≥10 kg	1 mmol/kg/day up to 40 mmol/day	≤0.67 mcg/kg/day
Adults and pediatric patients ≥12 years old	20 to 40 mmol/day	≤0.67 mcg/kg/day

Abbreviations: mmol = millimoles

5.3.3. Safety Assessment of Extractables/Leachables

Extractable studies were performed for the container closure system ((b) (4) stopper, (b) (4) vials supplied by (b) (4), and vial labels) using solvents of varying polarity and pH, with high temperature incubation and exaggerated surface area to volume ratios. Organic compounds discovered from the container closure components included (b) (4) among others, while no specific inorganic elements were found.

A leachable simulation study was conducted in 5-mL and 50-mL vials to reveal all potential leachables in the presence of Potassium Phosphates Injection, USP in the intended container closure system. The study targeted the compounds identified in the extractable analysis in addition to looking for any other compounds to determine the type and amount of compounds that could leach into the product. The analytical evaluation threshold (AET) was set at (b) (4) mcg/mL for all leachables identified in the study using 5-mL vials based on a worst-case toxicity assumption that any organic leachable compound discovered has genotoxic/carcinogenic potential, setting a product-specific threshold of toxicological concern (TTC) of (b) (4) µg/vial per leachable compound, and applying an additional (b) (4) safety factor ([(b) (4) mcg/vial) / (5 mL/vial)] x ((b) (4) safety factor) = (b) (4) mcg/mL).

To predict the leachable levels at the end of the proposed 2-year shelf life, assuming a worst-case linear accumulation of leachable migrants based on the incubation period of 55°C for 4 weeks, the final AET of each leachable was set at (b) (4) AET. No leachable compounds were identified at a level above (b) (4) AET. Therefore, there is no safety concern for the identified leachables. Overall, the leachable profile associated with the drug product container closure system appears to be acceptable.

6. Clinical Pharmacology

6.1. Executive Summary

The Applicant proposes Potassium Phosphates Injection, USP, phosphorus 3 mmol/mL, and potassium 4.4 mEq/mL, in three separate presentations (single-dose vials of 5 mL, 15 mL, and 50-mL Pharmacy Bulk Package vial) for approval under the 505(b)(2) pathway relying on the Agency's findings of safety and effectiveness for the two LDs:

- Sodium Phosphates Injection, USP, phosphorus 45 mmol/15 mL (3 mmol/mL), and sodium 60 mEq/15 mL (4 mEq/mL), approved under NDA 018892
- Potassium Chloride Injection, potassium per container (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), approved under NDA 020161

As discussed in Section 1 of this review, reliance on the LD Potassium Chloride Injection supports the safety of the potassium salt in the proposed product.

The Applicant has also provided literature data to support efficacy, safety, and dosing, for both phosphorus (active moiety) and potassium (salt) in the proposed product. The Applicant has not conducted new clinical pharmacology studies using the proposed product to support this submission.

Sodium Phosphates Injection, USP (NDA 018892) is approved in adults and pediatric patients including neonates, infants, children, and adolescents.

In the LD labeling of Sodium Phosphates Injection, the phosphorus dose and rate of administration are not specified for correction of hypophosphatemia for any age group. For PN, the LD's recommendation does not distinguish between adults and pediatric patients except for infants. The LD labeling states that approximately 12 to 15 mmol of phosphorus per liter bottle of PN solution containing 250 g dextrose is usually adequate to maintain normal serum phosphorus, though larger amounts may be required and the suggested dose for infants receiving PN is phosphorus 1.5 to 2 mmol/kg/day. Therefore, published literature provided additional support for the specific dosing recommendations for the proposed potassium phosphate product for both indications.

6.1.1. Recommendations

From a clinical pharmacology standpoint, the NDA is acceptable to support the approval of Potassium Phosphates Injection, USP for both indications in adult and pediatric patients.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. General Dosing and Therapeutic Individualization

General Dosing

The dose and rate of infusion of the proposed Potassium Phosphates Injection, USP should be dependent on the individual needs of the patient for both correction of hypophosphatemia and administration in PN.

Compared to the LD Sodium Phosphates Injection, USP, the proposed product Potassium Phosphates Injection, USP has a different salt form. Because of a risk for hyperkalemia due to the potassium salt, which can cause significant morbidity and mortality, the dosing of the proposed product needs to take both potassium and phosphate concentrations in patients into consideration. The labeling will state that the proposed product should not be used in intravenous fluids to correct hypophosphatemia in patients with serum potassium level ≥4 mEq/dL due to a concern of hyperkalemia.

The recommended dosages for both correction of hypophosphatemia and for PN are primarily based on published literature. Refer to Section 8.1.1 and Section 8.1.2 in this review for detailed review of published literature that supports the dosing recommendations. Dose recommendations are summarized.

<u>For Correction of Hypophosphatemia in Intravenous Fluids</u>

The recommended phosphorus doses (see Section 11) for an initial or single dose are body weight-based and dependent on the patient's serum phosphorus concentrations. Following the initial dose, additional dose(s) within a day or over several days may be needed in some patients until normalization of serum phosphorus concentrations, depending on the patient clinical needs as well as the serum phosphorus, calcium, and potassium concentrations. The same body weight-based dosage is recommended for pediatric patients as for adults, when considering that there appears to be no fundamental difference between adult and pediatric populations in the manifestations of hypophosphatemia or the physiology of phosphorus repletion.

The recommended maximum single dose is phosphorus 45 mmol (potassium 66 mEq). Greater than 50 mmol of phosphorus given as Potassium Phosphates Injection, USP has resulted in hyperphosphatemia, hypocalcemia, hyperkalemia, and calcium/phosphate precipitation in cases reported in published literature. In addition, literature supports a maximum initial or single dose of 45 (b) (4) mmol phosphorus in adults, followed by repeat assessment of the patient. See Section 11 for the recommended dosage regimen for all age groups (birth to adult).

The infusion rate of the proposed product is dependent on the administration route, i.e., through a peripheral or central venous catheter. The infusion rates are up to phosphorus 6.8 mmol/hour (potassium 10 mEq/hour) infused peripherally and phosphorus 15 mmol/hour (potassium 22 mEq/hour) infused centrally, respectively, in adults and pediatric patients 12

years and older. For infusion rates higher than 10 mEq/hour potassium in adults and pediatric patients weighing ≥20 kg and 0.5 mEq/kg/hour in pediatric patients weighing <20 kg, infusion through central venous catheter and continuous electrocardiographic (ECG) monitoring are recommended.

For Use in Parenteral Nutrition

A dosage of 20 to 40 mmol/day of phosphorus in adults and pediatric patients 12 years of age and older is generally recommended. For pediatric patients less than 12 years old, body weight-based phosphorus doses are recommended. See Section 11 for the recommended dosage regimen for all age groups (birth to adult).

Therapeutic Individualization

The dosage of Potassium Phosphates Injection, USP should be individualized based on the clinical needs of the patient for both indications and take into account the contribution of phosphorus and potassium from other sources. The dosage is adjusted based on serum phosphorus, and clinical status. Monitoring of serum phosphorus and potassium concentrations before and during treatment is recommended.

Outstanding Issues

There are no outstanding issues that preclude the approval of Potassium Phosphates Injection, USP from a clinical pharmacology perspective.

6.2.1. Pharmacology and Clinical Pharmacokinetics

The clinical pharmacology information for phosphorus is primarily based on the labeling of the LD, Sodium Phosphates Injection, USP. Additional information from the literature has also been submitted and reviewed.

Pharmacology

Phosphorus, present in large amounts in erythrocytes and other tissue cells, plays a significant intracellular role in the synthesis of high energy organic phosphates. It has been shown to be essential to maintain red cell glucose utilization, lactate production, and the concentration of both erythrocyte ATP and 2,3 diphosphoglycerate, and must be deemed as important to other tissue cells.

Per the LD labeling, intravenous infusion of inorganic phosphorus may be accompanied by a decrease in the serum level and urinary excretion of calcium.

As discussed in Section 2.1.2 of this review, the normal reference range for serum phosphorus in healthy adults is approximately 2.5 to 4.5 mg/dL and may vary depending upon the laboratory's reference range. In preterm and term infants less than 1 year of age, the lower end of the reference range reported is approximately 4 mg/dL. Pediatric patients 1 year to <18 years have a range similar to that of adults.

Pharmacokinetics

Clinical pharmacokinetics data for phosphorus using the proposed product are not available, as the Applicant did not conduct any pharmacokinetic studies.

Based on the LD labeling, intravenously infused phosphorus not taken up by the tissues is excreted almost entirely in the urine. Plasma phosphorus is believed to be filterable by the renal glomeruli, and the major portion of filtered phosphorus (greater than 80%) is actively reabsorbed by the tubules.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Pharmacology

Phosphorus, present in large amounts in erythrocytes and other tissue cells, plays a significant intracellular role in the synthesis of high energy organic phosphates. It has been shown to be essential to maintain red cell glucose utilization, lactate production, the concentration of both erythrocyte ATP and 2,3 diphosphoglycerate, and must be deemed as important to other tissue cells.

Pharmacokinetics of Phosphorus

Distribution

Approximately 85% of serum phosphorus is free and ultrafilterable and 15% is bound to protein.

Elimination

Intravenously infused phosphates not taken up by the tissues are excreted almost entirely in the urine. Serum phosphorus is filterable by the renal glomeruli with greater than 80% of filtered phosphorus actively reabsorbed by the proximal tubules, resulting in approximately 12.5% of glomerular filtrate excreted in the urine (Favus et al. 2006). Serum phosphorus levels are largely dependent on efficiency of reabsorption of filtered phosphorus.

Pharmacokinetics of Potassium

Potassium is freely filtered by the glomeruli, followed by the bulk of filtered potassium being reabsorbed in the proximal tubule, and less than 10% of filtered potassium is secreted in the distal tubule to urine (Palmer 2015).

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

The effectiveness of Potassium Phosphates Injection, USP, phosphorus 3 mmol/mL and potassium 4.4 mEq/mL), in intravenous fluids to correct hypophosphatemia and as a source of phosphorus in PN for adult and pediatric patients, is supported by reliance on the LD, i.e., Sodium Phosphates Injection, USP (NDA 018892).

The proposed product and the LD follow the same mechanism of action to provide repletion of phosphorus for correction of hypophosphatemia and to maintain serum phosphorus levels in the reference range for patients receiving PN. The efficacy for treatment or prevention of hypophosphatemia is based on phosphorus, which is dissociated from the salt form upon intravenous administration. Therefore, it is reasonable to rely the effectiveness of the proposed product on the LD despite differences in salt form.

No pharmacokinetic bridging is deemed necessary between the proposed product and the LD since both products are aqueous solutions for intravenous administration and the bioavailability of the phosphate from both products is self-evident. Refer to Section 4.2 in this review for additional comments on biobridge.

The LD has established safety and effectiveness in adult and pediatric patients (neonates, infants, children, and adolescents) to correct hypophosphatemia and in PN (Prescribing Information, Sodium Phosphate Injection, 2018). The Applicant seeks the same indications in the same patient populations as for the LD.

Refer to Section 8.1 in this review for more details on the efficacy evidence review.

6.3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed dosing regimens for both indications, based on the individual needs of the patient, are appropriate for the general patient population. There are no new clinical studies conducted with the proposed product. The dosing recommendations are based on the LD and the published literature.

<u>To Correct Hypophosphatemia</u>

The recommended dosage of Potassium Phosphates Injection, USP for an initial or single-dose range from 0.16 to 0.64 mmol/kg of phosphorus and is dependent on the patients' baseline serum phosphorus concentrations. This dosage range is derived from the available literature in adults (see Section 8.1.1).

It has been reported in the literature that potassium phosphates can be safely administered intravenously at an initial, or single, dose of phosphorus 0.2 to 0.64 mmol/kg in hypophosphatemic adults with normal blood calcium concentration and renal function. A single

dose of 1 mmol/kg, or more than 50 mmol, has been associated with serious ARs of hyperphosphatemia, hypocalcemia, and hyperkalemia in published literature. Therefore, the recommended dosage range is 0.16 to 0.64 mmol/kg, with a maximum of 45 mmol. Following the initial dose, additional dose(s) may be needed in some patients based on the patient clinical needs as well as on the serum phosphorus, calcium, and potassium concentrations.

The recommended dosage for pediatric patients is the same as that in adults. This recommendation is supported by the fact that there appear to be no fundamental differences between adult and pediatric patients in the manifestations of hypophosphatemia or the physiology of phosphorus repletion.

Because pain and thrombophlebitis are associated with peripheral infusion of potassium-containing solutions, including potassium chloride, the recommended maximum concentration for peripheral administration is phosphorus 6.8 mmol/100 mL (potassium 10 mEq/100 mL) in adults and pediatric patients 12 years of age and older and phosphorus 0.27 mmol/10 mL (potassium 0.4 mEq/10 mL) in pediatric patients less than 12 years of age. More concentrated solutions of phosphorus 18 mmol/100 mL (potassium 26.4 mEq/100 mL) and phosphorus 0.55 mmol/10 mL (potassium 0.8 mEq/10 mL), for adults and pediatric patients 12 years of age and older, and pediatric patients less than 12 years of age, respectively, can be infused through a central venous catheter, which is supported by guidelines and publications.

For pediatric patients less than 12 years of age, the smallest recommended volume should be used, considering the maximum concentration for peripheral and central administration, as described above for older pediatrics and adults. See Section15.4 for discussion of fluid requirements and maximum potassium concentrations for peripheral and central administration in neonates.

Due to the risk of serious ARs, including cardiac arrhythmias and death, the maximum recommended infusion rate for adults and pediatric patients 12 years of age and older is phosphorus 6.8 mmol/hour (potassium 10 mEq/hour) when infused peripherally and phosphorus 15 mmol/hour (potassium 22 mEq/hour) when infused centrally. These maximum rates are generally recommended by practice guidelines in adults and pediatric patients 12 years of age and older. The recommended maximum peripheral infusion rate of potassium 10 mEq/hour for the proposed product is consistent with that for LD Potassium Chloride Injection, i.e., usually not exceeding 10 mEq/hour or 200 mEq for a 24-hour period if the serum potassium level is greater than 2.5 mEq/L.

Continuous ECG monitoring and infusion through a central venous catheter is recommended for infusion rates higher than:

- Potassium 10 mEq/hour for adults and pediatric patients weighing 20 kg or greater
- Potassium 0.5 mEq/kg/hour for pediatric patients weighing less than 20 kg

As noted above, there is no recommendation for a maximum infusion rate for the proposed product in young children less than 12 years of age because this information for either phosphorus or potassium is not available. Due to the long-standing intravenous use of

sodium/potassium phosphates in clinical practice, it is expected that individual medical institutions will have their own standards for infusion which will safeguard patients.

Parenteral Nutrition

The recommended dosage for Potassium Phosphates Injection, USP of 20 to 40 mmol/day of phosphorus in both adults and pediatric patients 12 years of age and older, is supported by the labeling of LD Sodium Phosphate Injection, clinical guidelines and published literature. The dosage should be individualized based upon the patient's clinical condition, nutritional requirements, and the contribution of oral or enteral phosphorus and potassium intake.

In the LD Sodium Phosphate Injection label, phosphorus 12 to 15 mmol/250 g dextrose (equated to 35 to 45 mmol/day assuming a typical daily diet of 2500 calories) is recommended. This phosphorus dose approximates the dosage range of 20 to 40 mmol/day recommended by ASPEN guidelines for adults. Per ASPEN guidelines, dose of 10 to 40 mmol/day is recommended in adolescents and children weighing at least 50 kg. Since pediatric patients 12 years of age and older have the same daily phosphorus requirement as adults, it is appropriate to recommend a simplified dosing for adults and pediatric patients 12 years of age and older.

The recommended body weight-based doses in younger children, i.e., phosphorus 2 mmol/kg/day in pediatric patients up to 1 year of age and phosphorus 1 mmol/kg/day (up to 40 mmol/day) in pediatric patients >1 to <12 years of age, are supported by the approved labeling for the LD Sodium Phosphates Injection, USP; daily requirements by 21 CFR 101 Food Labeling (Nutrition and Supplement Facts); clinical guidelines; and clinical studies in publications. In the approved labeling for Sodium Phosphate Injection, the suggested dose of phosphorus for infants receiving TPN is 1.5 to 2 mmol/kg/day. The recommendation on the maximum dose of 40 mmol for pediatric patients >1 to <12 years of age will align this population with adults and older children.

Dosing Consideration for Safety of Potassium

It is known that rapid intravenous administration of potassium-containing products can cause significant morbidity and mortality related to hyperkalemia. Therefore, the administration of potassium phosphates, which is also a source for potassium clinically (although not indicated for repletion of potassium), must consider the dose and infusion rate of potassium accompanying the active moiety of phosphates, as well as factors such as the baseline serum potassium level, renal function of the patients, clinical status, and concomitant medications that can alter the serum potassium level.

For hypophosphatemia correction, the recommended maximum single dose of the proposed product contains 66 mEq potassium. At this maximum single dose, the daily potassium dose is unlikely to be higher than the maximum approved dose for the LD, Potassium Chloride Injection, i.e., 200 mEq potassium for a 24-hour period, if the patient's baseline serum potassium level is greater than 2.5 mEq/L.

In addition, the recommended infusion rates of phosphorus not exceeding 6.8 mmol/hour via a peripheral line in an unmonitored patient would limit the potassium infusion rates to 10 mEq/hour, which is acceptable and consistent with current clinical practice guidelines for potassium use as well as the labeling for the LD Potassium Chloride Injection. For the LD Potassium Chloride Injection, the recommended infusion rates should not usually exceed 10 mEq/hour (if the serum potassium level is greater than 2.5 mEq/L) and up to 40 mEq/hour (in urgent cases with continuous monitoring of the ECG and frequent serum potassium determinations).

Furthermore, in general, the proposed product will be administered in intravenous fluid to correct hypophosphatemia only when the baseline serum potassium is <4 mEq/dL, to avoid hyperkalemia. For hypophosphatemia correction, an alternative source for parenteral phosphate such as sodium phosphate product should be used for patients with a serum potassium level ≥4 mEq/dL.

Refer to Section 8.2.4.1 for additional discussions on the safety of potassium.

6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Renal Impairment

There were no pharmacokinetics studies in patients with renal impairment for the proposed product to evaluate the effects of renal impairment on the phosphorus concentrations after administration of potassium phosphate and to inform the dosage for patients with renal impairment. However, since potassium and phosphorus are substantially excreted by the kidney, the risk of hyperkalemia and hyperphosphatemia with the proposed product is considered greater in patients with impaired renal function.

Therefore, generally, dosing in patients with renal impairment should be cautious. Starting the initial dose at the low end of the dosing range is recommended in patients with moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73 m^2), with monitoring of serum phosphorus potassium, calcium, and magnesium concentrations.

The proposed product is contraindicated in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) or end-stage renal disease (ESRD) because of the risk for hyperphosphatemia and hyperkalemia.

Geriatric Patients

Since elderly patients have greater frequency of decreased renal function, caution is advised in dosing and starting at the low end of the dosing range is recommended, in addition to monitoring of renal function.

6.3.2.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

There are no clinically relevant food-drug interactions because the proposed product is administered by intravenous infusion.

There were no clinical studies conducted for drug-drug interactions. Nevertheless, a potentially clinically relevant additive increase in serum potassium concentrations is possible when the proposed product is given with drugs that increase serum potassium concentrations, especially when renal function is compromised. The following are the drug classes that can increase serum potassium concentrations by affecting potassium homeostasis.

- Potassium-sparing diuretics such as amiloride, triamterene, and spironolactones can increase potassium retention by reducing renal elimination of potassium and hence produce severe hyperkalemia (Horisberger and Giebisch 1987).
- Renin-angiotensin-aldosterone system inhibitors, such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), aldosterone receptor antagonists (ARAs), and direct renin inhibitors (DRIs), e.g., aliskiren, are associated with an increased risk of hyperkalemia. ACEIs, ARBs, and DRIs increase serum potassium levels by interfering with angiotensin II-mediated stimulation of aldosterone secretion from the adrenal gland and by decreasing renal blood flow and GFR in special patient populations. ARAs increase serum potassium levels by blocking interaction of aldosterone with its receptor, reducing renal potassium excretion (Weir and Rolfe 2010).
- Calcineurin inhibitors (CNIs) such as cyclosporine and tacrolimus may reduce potassium excretion by altering the function of several transporters, decreasing the activity of the renin-angiotensin-aldosterone system, and impairing tubular responsiveness to aldosterone (Lee and Kim 2007).
- Nonsteroidal anti-inflammatory drugs such as ketorolac may cause hyperkalemia by suppression of aldosterone secretion following inhibition of prostaglandin inhibition (Pearce et al. 1993; Schlondorff 1993; Kim and Joo 2007; Lafrance and Miller 2012; Nash et al. 2019).
- Trimethoprim reduces renal potassium excretion by competitively inhibiting the sodium channels of the epithelium in the renal distal tubules (Perazella and Mahnensmith 1996; Nickels et al. 2012).
- Digitalis compounds such as digoxin may inhibit the sodium/potassium ATPase pump leading to an increase in serum potassium levels (Glynn 1964; Papadakis et al. 1985).

Therefore, co-administration of the proposed product with the drug classes increasing serum potassium levels should be avoided due to the risk of hyperkalemia. If use cannot be avoided, serum potassium concentration should be closely monitored. Inclusion of examples for such drug classes increasing serum potassium levels is recommended in the labeling.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The safety and efficacy of Potassium Phosphates Injection, USP is based upon the findings of safety and effectiveness of the LD, Sodium Phosphates Injection, USP. The following tables include additional published clinical data to support the safety, efficacy, and dosing of potassium phosphates in intravenous fluids for the correction of hypophosphatemia and use in PN.

Correction of Hypophosphatemia

Table 5: A summary of the nine clinical studies considered to represent the best evidence from the literature to support dosing of intravenous potassium phosphates for the correction of hypophosphatemia in adult patients. These studies include both efficacy and safety information and were conducted in 128 adult patients who received intravenous potassium and/or sodium phosphates as a single- or multiple-dose regimen up to 7 days.

Table 6: A summary of six publications that provide additional supportive prospective and retrospective clinical data to support efficacy, safety, and dosing of intravenous potassium phosphates for the correction of hypophosphatemia. Five of the publications contain information from adult patients and one publication in pediatric patients (1.7 to 8.8 years) is also included.

Use in PN

Table 7: Two clinical studies support the efficacy, safety, and dosing of potassium phosphates in PN in adult patients.

Table 8: A summary of two clinical studies of preterm and term neonates (one retrospective; one prospective) receiving various enteral and parenteral nutritional formulas, including phosphorus supplementation in PN. The dosage of phosphorus that patients received is included in the study as observational data.

Table 5. Best Available Published Data From Clinical Trials in Adult Patients to Support Efficacy, Safety, and Dosing of Potassium Phosphates in Intravenous Fluids to Correct Hypophosphatemia

Ref.	Design (Drug)	Population	Doses/Duration*	Outcomes	Complications/AEs
Vannatta (1981)	Open-label, prospective (KH_2PO_4)	10 adults with phosphorus (P)≤1 mmol/dL, normal or low K^+ and no RI	9 mmol P q12h up to 48h; Ca^+, P, and K^+ measured q12h	All pts responded, with P>1 mg/dL at 36h and normal in 6 pts at 48h	1 pt with hyperP; 1 pt with decreased Ca^+ asymptomatic; 8 pts with low Mg^+
Vannatta (1983)	Case series (KH_2PO_4)	10 adults with P≤1mmol/dL, no RI, normal Ca+	0.32 mmol/Kg q12h until P≥2 mg/dL 1 pt got 0.48 mmol/Kg/12h; P, K^+, Mg^+, Ca^+ measured at 6 and 12h and then q12h	Response quicker with higher dose, but variable; higher dose required in 1 pt with very low P level who responded to higher dose	No hyperP; hypoCa $^+$7 pts (70%); Ca^+ values at 6, 12, 24, 36, and 48h post-tx serum Ca^+ levels below 8.5 mg/dL (range 7.0-8.3) in 7 of 10 pts; 6 of these 7 pts had pre-tx serum Ca <8.5 mg/dL; all pts asymptomatic and hypocalcemia not clinically significant; 4/10 pts concomitant hypoMg^+
Kingston (1985)	Open-label, prospective, ICU (sodium phosphates [N=17] or potassium phosphates [N=14])	31 hypoP adults, 2 with RI	10 to 15 mmol P; mean 0.3 mmol/kg (over 4h); range 0.19-0.8 mmol/kg (over 4h)	All pts responded with increased P; mean P rise from 0.88±0.4 mg/dL to 2.3±0.9 mg/dL; no change in Ca^+, Mg^+, blood pressure	No arrhythmias; baseline, 10 pts hypoCa^+, 10 hypoMg^+, 6 hypoK^+; 1 pt (3%) “showed transient deterioration in renal function in the 2 days after phosphorus infusion and this may have been due to septicemia”; no significant change in mean serum Ca^+
Clark (1995)	Open-label, prospective, ICU (sodium or potassium phosphates)	78 adults on PN, P<3 mg/dL, no RI, no obesity, normal Ca+	mild 2.3 to 3 mg/dL – 0.16 mmol/kg mod 1.6 to 2.2 mg/dL – 0.32 mmol/kg severe <1.5 mg/dL – 0.64 mmol/kg In 100 cc over 4-6h; single dose; P, Ca^+, Mg^+, albumin, BUN, creatinine measured daily x 3 days	67 completed: 31 mild, 22 mod, 14 severe; all responded to tx; other labs remained normal, no AEs	No clinically significant adverse effects; no clinically significant adverse events, nor changes in other serum/blood electrolytes concentrations in response to the phosphorus dose

Ref.	Design (Drug)	Population	Doses/Duration*	Outcomes	Complications/AEs
Rosen (1995)	Open-label, prospective, ICU (sodium or potassium phosphates)	11 adults, P<2 mg/dL, normal Ca^+, not pregnant or BF; excluded creatinine clearance <10 mL/min, creatine >4, BUN >80, u/o <30mL/h	15 mmol P over 2h, K+P if K^+ ≤3.5 mg/dL, NaP[9] if K^+ >3.5 mg/dL 2nd dose if P<2 mg/dL at 6h, 3rd dose if remained low at 18-24 h, Max dose 45 mmol/24h	11 completed, all P>1 and <2 mg/dL post-tx, all pts responded, 3 required more than one dose	No clinically significant adverse events No significant changes noted in serum calcium, magnesium or potassium concentrations, urine output, vital signs, or reflexes
Perreault (1997)	Open-label, prospective, ICU (potassium phosphates (providing 22 mmol K/15 mmol P))	37 Adults P<2.48 mg/dL, central access, Excluded K^+4.8 mEq/L, Addison's dz., Ca^+<6.4 mg/dL and product of Ca^+ and P<60 mg^2/dL^2	Group 1: P 1.27 to 2.48 mg/dL, dose 15 mmol P (N=27) Group 2: P≤1.24 mg/dL, dose 30 mmol P (N=10) In IV fluids, stopped P-binding antacids; calories decreased to <35 Kcal/Kg/d; tx D/C if K^+>5.3 mEq/L or Ca^+>6.4 mg/dL	All pts responded, no hyper P, Group 1 - Normal P in 81% with one dose Group 2 – Normal P in 30% with one dose	No hyperphosphatemia, hyperkalemia, or significant arrhythmia Significant drop in total serum calcium, concentrations occurred in 2 pts who were slightly hypercalcemic prior to the infusion. Serum calcium concentrations remained above normal and this was not associated with any adverse effects 7 pts with recurrence of hypoP
Charron (2003)	Open-label prospective, dose randomized, ICU (not specified)	32 adults with P<2 mg/dL; excluded significant RI, hyper Ca^+, phosphorus phosphorus/calcium product >4.5 $mmol^2/L^2$ (>55 mg^2/dL^2), K^+ >4.5 mg/dL; some pts also receiving P in PN (# not specified)	Mod - P<2 to >1.2 mg/dL – either 30 mmol over 2h or 30 mmol over 4h Severe - <1.2 mg/dL either 45 mmol over 1h or 45 mmol over 6h	98% response rate to P>2 mg/dL at end of infusion; hypoP reoccurred at 24h in 28%	5 pts with hyper P 8 with K^+ >5 mEq/L (max K 6.1 mEq/L) asymptomatic Electrolytes, blood gas, renal function monitored and stable, hypoP reoccurred at 24h in 28%

Ref.	Design (Drug)	Population	Doses/Duration*	Outcomes	Complications/AEs
Taylor (2004)	Open-label retro- and prospective, ICU, retrospective control (sodium or potassium phosphates)	111 adults with P<2.2 mg/dL, excluded if calculated creatine clearance <25 mL/min, creatine >4 mg/dL, u/o <30 cc/2h, corrected Ca^+ <7.5 mg/dL, on PN with P, weight >120 or <40 Kg	Phosphorus dosed in IV fluids: **Phosphorus level** / **Weight 40-60 kg** / **Weight 61-80 kg** / **Weight 81-120 kg** <1.0 mg/dL: 30 mmol / 40 mmol / 50 mmol 1.0-1.7 mg/dL: 20 mmol / 30 mmol / 40 mmol 1.8-2.2 mg/dL: 10 mmol / 15 mmol / 20 mmol Source: Article Table 1 If the pt's potassium is <4.0 use potassium phosphorus; if the pt's potassium is >4.0 use sodium phosphorus	Retrospective: Success in P repletion (53% in moderate pts; 27% in severe pts) Prospective: 84 (76%) reaching normal P after single dose (78% in mod., 63% in severe); 7 pts required 3 or more doses to achieve normal P	None developed hyperP after repletion in either the retrospective or prospective groups; no new electrolyte disturbances were detected in pts who received supplementation per protocol
Brown (2006)	Open-label prospective, ICU (sodium or potassium phosphates)	79 adults with P<3.0 mg/dL: excluded acute renal failure, chronic kidney disease, creatinine clearance <30mL/min^2, abnormal Ca^+, BMI >40 Kg/m^2 in pts on PN	Mild: >2.3-3.0 mg/dL, 0.32 mmol/kg [N=34] Mod: 1.6-2.3 mg/dL, 0.64 mmol/Kg [N=30] Severe: ≤1.5 mg/dL, 1 mmol/kg [N=15] K+P used if K ≤4 mEq/dL and NaP used if K ≥4 mEq/dL; up to two daily doses, infused at ≤7.5 mmol/hr	All pts responded; mean serum P normal on Day 2 in mod. and severe groups; normal in all groups on Day 3	HypoCa $^+$5% [N=4], hyperP 10% [N=8], asymptomatic; Mg^+, sodium, and K^+ and Ca^+ as well as arterial pH, were stable across the study; no AEs

Abbreviations: AE = adverse event; BF = breast feeding; BMI = body mass index; BUN = blood urea nitrogen; Ca^+ = calcium; h = hour; ICU = intensive care unit; IV = intravenous; K^+ = potassium; K+P = potassium phosphates injection; mEq = milliequivalents; Mg^+ = magnesium; mmol = millimoles; NaP = sodium phosphates injection; P = phosphorus; PN = parenteral nutrition; pt = patient; RI = renal insufficiency; tx = treatment; u/o = urine output
*Normal references ranges used for phosphorus were not specified in these articles
Source: Submitted by Applicant

Table 6. Additional Published Clinical Data in Adult and Pediatric Patients to Support Efficacy, Safety, and Dosing of Potassium Phosphates Intravenous Fluids to Correct Hypophosphatemia

Ref.	Design (Drug)	Population	Doses	Outcomes	Complications	Comments
O'Connor (1977)	Open-label prospective (case report)	P<2 mg/dL and Ca+ >7 mg/dL, no ESRD, had cardiac catheter in place for other reasons; Adults	~32 mmol K+P in 60 mL sterile water over 8h	Mean left ventricular stroke work for these pts increased from 49.57 to 71.71 g-m per beat (P<0.01)		Improved cardiac output with P normalization.
Lee (1978)	Retrospective (case reports)	3 pts with profound coma and hypoP; adults	Varied 40–45 mmol	2/3 with mental status improved with P repletion		Supports potential for improved mental status.
Wilson (1982)	Open-label, randomized (sodium phosphates)	44 pts with DKA randomized to 3 doses, mean age 27; adults and peds	Not given P [N=15] 15 mmol Na+P [N=17] 15 mmol Na+P X 3 doses [N=15]	Measurements at 24h showed [P] <1.5 mg/dL in 6, 3, and 1 pt(s) from Groups 1, 2, and 3, respectively	One death in each group; no hemolysis, cardiomyopathy, or liver dysfunction.	Supports need for frequent monitoring of P in pts with DKA.
Andress (1984)	Open-label, prospective (intravenous phosphorus (NOS))	11 adults, P<1 mg/dL, no RI, u/o >30 cc/h	0.32–0.48 mmol/kg/ over 12 h, continued until P≥2 mg/dL	An inverse correlation was found between serum P and plasma 1,25(OH)2D (r=-0.62, P<0.005)		No significant change in [Ca] or [Mg].
Bech (2013)	Open-label, prospective (sodium-potassium phosphates (providing 12.5 mmol K/15 mmol P))	50 adults with P<0.6 mmol/L	Dose calculated: 0.5 x body weight x (1.25 - [serum P]) = dose P mmol/L. Mean 28 mmol (range 16–52 mmol) infused at 10 mmol/hour	Post-infusion P levels were >0.6 mmol/L in 98% of the pts.;1/3 developed recurrent hypoP	hyperkalemia [N=1] in pt enrolled outside protocol criteria with baseline K 5.0 mEq/L; otherwise, no hyperP or hyperK.	Weight-based dosing but baseline serum P levels not taken into consideration with dosing.
Leite (2017)	Retrospective study; pediatric pts; mean age of 5.4 years (range 1.7–8.8 years)	78 children with severe burns were assessed for serum P for the first 10 days of stay in ICU	P was provided to all children as part of enteral feeds but was not routinely supplemented; IV supplementation was also administered when the serum P was <3 mg/dL	Pts on enteral feeds received a mean phosphorus enteral dose of 1.08±0.76 mmol/kg/day. Forty-three children received IV phosphate replacement at a mean dose of 1.05±0.5 mmol/kg/day	HypoP was observed in 62 (80%); significantly lower PO_4 values were observed on Days 2, 3, and 4.	Definition of hypoP Serum P <3.8 mg/dL for children age ≤2 years and <3.5 for children ≥3 years.

Abbreviations: Ca^+ = calcium; DKA = diabetic ketoacidosis; ESRD = end-stage renal disease; ICU = intensive care unit; IV – intravenous; K+P = potassium phosphates injection; Mg^+ = magnesium; mmol = millimoles; NA = sodium; NOS = not otherwise specified; P = phosphorus; pts = patients; RI = renal insufficiency
Source: Reviewer Table

Table 7. Published Clinical Study in Adult Patients of the Dosing, Efficacy and Safety of Potassium Phosphates in Parenteral Nutrition

Ref.	Design/Drug	Population	Doses	Outcomes	Complications	Comments
Sheldon (1975)	Randomized, open-label/potassium phosphates	Adult trauma pts, no RI, normal P level before PN started	Dosed in PN Group A: no Ca or P Group B: <15 mEq P/ 1000 cal/day Group C: 15–25 mEq P/100 cal/day Group D: >25 mEq P/1000 cal/day	When hypoP occurred (<1 mg/dL) pts were tx'ed with P in PN. Group A: All 8 pts with hypoP in 3 to 5 days. Group B: All 5 pts hypoP in 1 to 7 days Group C: All remained normal P Group D: 14 pts, some hyperP (# not specified).	None reported; none with symptoms of hypoP	Recommended 20–25 mEq potassium phosphates per 1000 nonprotein cal (14–17 mmol phos/1000 cal).
Pigon (1985)	Open-label randomized 1:1, ICU/sodium-potassium phosphate (KabiVitrum 4851)	30 adults, on PN Dose decreased for RI	Group 1: 7.5 mmol/day from phospholipids [N=16] Group 2: 40 mmol (N=1) or 80 mmol (N=11) added to glucose solution and administered by central vein over 12 to 14h [N=12]	Group 1: 3 developed hypoP Group 2: All within normal range except 3 with hyperP in high-dose group.	No adverse reactions. Group 1: hypoP (N=3) Group 2: hyperP (N=3)	No hypoCa^{+} but Ca lower in Group 2; no renal failure; dose was not individualized.

Abbreviations: Ca – calcium; ICU = intensive care unit; mEq = milliequivalents; mmol = millimoles; P = phosphorus; PN = parenteral nutrition; pts = patients; RI = renal insufficiency

Table 8. Published Clinical Data in Pediatric Patients to Support Efficacy, Safety, and Dosing of Potassium Phosphates in Parenteral Nutrition

Ref.	Design/Drug	Population	Doses	Outcomes	Key Findings	Complications	Comments
Moltu et al. (2013)	Prospective trial; 50 VLBW infants (enrolled within 24 hours of birth and followed for the 1st 4 weeks of life) randomized to intervention [high protein and energy] (energy, protein, fat, AA, DHA, and vitamin A), but not randomized to phosphorus dose (n=24) and control [standard feeding protocol] (n=26).	50 VLBW infants weighing <1500 grams	Intervention group: Observed phosphorus dose was 2.3 (1.9–2.5) mmol/Kg/day. Control group: Observed 2.4 (2.3–2.4) mmol/Kg/day. Preterm infants received human milk, enteral nutrition, and were also supplemented with parenteral nutrition.	77% infants in the intervention group had hypophosphatemia compared to 19% infants in control group.	Enhanced supply of energy, protein, essential fatty acids, and vitamin A caused postnatal growth along the birth percentiles for both weight and head circumference. There was no discussion of differences in hypophosphatemia between the two groups. The higher energy supply in the intervention group possibly contributed to more refeeding syndrome and thus more hypophosphatemia.	Intervention group had higher incidence of septicemia; therefore, the study was terminated.	Generally, in clinical practice, the preterm infants are administered higher doses of phosphates (per weight).

Ref.	Design/Drug	Population	Doses	Outcomes	Key Findings	Complications	Comments
Mulla et al. (2017)	Retrospective cohort study of two groups born within two discrete 6-month periods (epochs). 51 preterm infants were enrolled to Epoch 1 (6/1 to 11/29/13) and 49 infants to Epoch 2 (12/1/13 to 5/31/14). Results from this study are based on P administered in the first week of postnatal life.	Preterm infants given PN in first postnatal week. Population in both Epochs were similar at baseline for gestational age, birth weight, gender; small for gestational age, time when PN was started, and number of days PN was administered.	Epoch 1: Pts received 1.7 mmol Ca^{2+} and 1.1 mmol PO_4 per 100 mL of PN (including P contributed by lipids) = phosphorus 0.8 to 1.4 mmol/kg/day. Epoch 2: Pts received 1.7 mmol/ Ca^{2+} and 1.7 mmol P per 100 mL of PN (less the P contribution from lipid), P was added using sodium glycerophosphate (Fresenius Kabi, Runcorn, UK) containing phosphate 20 mmol and Na^{4+}40 mmol per 20-mL vial) = phosphorus approximately 1.9 mmol/kg/day.	In Epoch 2, fewer babies experienced severe hypocalcemia; the nadir serum P concentrations were higher, fewer cases of hypophosphatemia, and hypokalemia were reported relative to Epoch 1.	The recommended Ca^{2+}: P ratio of 1.3:1 led to metabolic abnormalities.	Hypercalcemia, hypophosphatemia, and hypokalemia were observed in patients enrolled in Epoch 1	For preterm infants receiving higher amounts of amino acids (≥2.5 g/kg/day) in the first postnatal week, an equimolar (1:1) Ca^{2+}: P ratio appeared preferable to that currently recommended (1.3–1.7:1). There were no issues with PN compatibility with higher P administration and seemed well tolerated.

Abbreviations: AA = arachidonic acid; DHA = docosahexaenoic; P= phosphorus; PN = parenteral nutrition;; mmol = millimoles; VLBW = very low birth rate; ESPGHAN = European Society of Paediatric Gastroenterology, Hepatology and Nutrition
Source: Reviewer-generated table

7.2. Review Strategy

The Applicant supplied a list of published references to support the efficacy and safety of Potassium Phosphates Injection, USP for the correction of hypophosphatemia, but presented limited information about the methods used to identify these specific references. No publications were submitted specifically in support of the use in parenteral nutrition.

Of the references identified by the Applicant, 19 clinical studies were cited for adults and one in pediatrics that evaluated intravenous potassium phosphates dosing and administration algorithms for the treatment of hypophosphatemia.

The Division of Epidemiology I (DEPI I), Office of Surveillance and Epidemiology Review, Office of Pharmacovigilance and Epidemiology, assessed the literature presented in this NDA to support the safety or efficacy of Potassium Phosphates Injection, USP, and also performed an independent literature search and review.

Despite the lack of specified methodology for the Applicant's literature search, DEPI concluded that nine of the Applicant's literature articles may be considered "a reasonably complete representation of literature evidence available from prospective clinical studies of potassium phosphate IV for treatment of hypophosphatemia in adults."

See the DEPI review in Document Archiving, Reporting and Regulatory Tracking System (DARRTS) dated August 21, 2019, for an explanation of the methods used to assess the Applicant's literature search and for DEPI's complementary literature search.

Additional references included by the Applicant in the iPSP submission were also reviewed.

A summary of the published data determined to be most relevant to support both indications in adult and pediatric patients is included in the tables in Section 7.1. Additional discussion of these data and other sources of information used in the review is found below in Section 8.

8. Clinical Evaluation

8.1. Review of Evidence Used to Support Efficacy

8.1.1. Correction of Hypophosphatemia in Intravenous Fluids

8.1.1.1. Listed drug (LD)

The Applicant is relying upon the Agency's findings of safety and efficacy for Sodium Phosphates Injection, USP (NDA 018892).

The LD does not include a dosage regimen for any age group for the correction of hypophosphatemia indication. The Dosage and Administration section states "The dose and rate of administration are dependent upon the individual needs of the patient. Serum sodium, phosphorus, and calcium levels should be monitored as a guide to dosage."

The Pediatric Use subsection clarifies that the product is intended not only for adults but also for pediatric patients of all ages, noting that the safety and effectiveness of sodium phosphate has been established in pediatric patients (neonates, infants, children, and adolescents).

8.1.1.2. Relevant published clinical trials

The Applicant provided published literature to support efficacy for correction of hypophosphatemia in adults. The relevant trials are summarized in Table 5 and Table 6 above.

In general, the clinical trials of the intravenous use of phosphorus supplementation in intravenous fluids were open-label in design using changes in the patients' baseline serum phosphorus level pre- and post-treatment evidence of treatment response. These studies were not designed to formally evaluate clinical efficacy outcomes. Available published clinical trials were conducted under varying conditions; datasets and case report forms from these trials are not available for detailed review.

In general, the studies showed that the lower the baseline serum phosphorus levels, the higher the dose of phosphates required to achieve a post-treatment level in the normal reference range.

Adult Patients

Many of the clinical studies described in Table 5 use a graduated weight-based dosing regimen depending on the degree of baseline hypophosphatemia ranging from approximately 0.16 to 1 mmol/kg. In some of the studies, the specified maximum dose was 45 to 50 mmol. Historically, doses higher than 50 mmol infused over 3 hours or less have been associated with serious AEs of hyperphosphatemia, hyperkalemia, and hypocalcemia (Shackney and Hasson 1967).

The trials allowed for additional doses and repeat assessment of the patient, including monitoring of serum phosphorus, potassium, and calcium levels prior to administration of additional doses.

A maximal daily dose of phosphorus was not described in these studies, as phosphorus should be repleted until normal serum levels are obtained and sustained.

Pediatric Patients

A few publications identified prevalence of hypophosphatemia in critically ill pediatric patients; however, only one publication (Leite et al. 2017) provided observational information on doses used for correcting hypophosphatemia.

The efficacy and necessity of maintaining normal serum phosphorus levels is supported by the known physiology and daily requirements in children, and the current clinical experience and literature-supported practice guidelines (Greene et al. 1988; Koletzko et al. 2005; SickKids Nutrition Team 2007; Wolfsdorf et al. 2014; Mihatsch et al. 2018).

Normal serum phosphorus concentrations are higher in children, and thus, reference range cutoff values for children is higher. Hypophosphatemia in pediatric patients is generally defined as a serum phosphorus concentration less than 4 mg/dL; severe hypophosphatemia is generally defined as serum phosphorus concentrations less than 1 to 1.5 mg/dL. However, there is no consensus definition for degrees of severity of hypophosphatemia in pediatric patients.

Summary of Dosing

There appears to be no fundamental difference between adult and pediatric populations in the manifestations of hypophosphatemia. The physiology of phosphorus repletion also appears to be essentially the same in all ages.

The literature supports an initial, or single, dose of 0.16 mmol/kg to 1 mmol/kg and a maximum of 45 mmol phosphorus in adults, followed by repeat assessment of the patient, including serum phosphorus, potassium, and calcium levels prior to administration of additional doses.

The total daily dose of Potassium Phosphates Injection, USP is limited by the maximal recommended daily dose of potassium, which is generally 200 mEq/day. A higher potassium dosage may be tolerated in severely hypokalemic patients.

See additional discussion on hyperkalemia in Section 8.2.4.1 of this review.

8.1.2. Use in Parenteral Nutrition

8.1.2.1. Listed drug

The approved labeling for Sodium Phosphates Injection, USP (NDA 18892) does not distinguish between adults and pediatric patients for use in PN; the only age subgroup with a distinct dosing recommendation is infants.

In patients on TPN, approximately 12 to 15 mM phosphorus (equivalent to 372 to 465 mg elemental phosphorus) per liter bottle of TPN solution containing 250 g dextrose is usually adequate to maintain normal serum phosphorus. The suggested dose of phosphorus for infants receiving TPN is 1.5 to 2 mM P/kg/day.

Note that the units of phosphorus in the approved labeling (mM) are incorrect. Instead, the dose of phosphorus should be expressed in units of mmol.

8.1.2.2. Daily phosphorus requirements

Institute of Medicine's (IOM's) Age-Based Reference Standards for Daily Phosphorus Intake

The Food and Nutrition Board of the IOM establishes guidelines for adequate dietary intake and provides documentation of the data used to derive the reference values (Institute of Medicine 1997).

The Recommended Dietary Allowance (RDA) is the average daily level of intake sufficient to meet the nutrient requirements for nearly all (97% to 98%) of healthy people. An "adequate intake" (AI) is established when evidence is insufficient to develop an RDA and is set at a level assumed to ensure nutritional adequacy. RDAs and AIs may both be used as goals for individual intake. For healthy breastfed infants, the AI is the mean intake.

The IOM states that, on a mixed diet of organic and inorganic phosphorus, the net absorption of total phosphorus ranges from 65% to 90% in infants and children and 55% to 70% in adults. Assuming an average bioavailability of 78% in infants and children and 65% in adults, the estimated weight-based dose for birth through 12 years of age ranges from approximately 0.5 to 1 mmol/kg (as shown in the final column of the table below).

Table 9. Estimated Weight-Based Dose for Birth Through 12 Years of Age

Age Group (IOM-defined months/years)	Weight (kg) 5th to 97th Percentile per CDC Growth Charts	AI (infants)* RDA in mmol Assuming Average Bioavailability	Calculated Weight-Based Daily Dosage Assuming Average Bioavailability
Infants 0 to 6 months	2.3 kg to 9.5 kg	2.5 mmol	0.3 to 1.1 mmol/kg
Infants 7 to 12 months	5.9 kg to 10.2 kg	7 mmol	0.7 to 1.2 mmol/kg
Children 1 to 3 years	8.2 kg to 17.9 kg	11.6 mmol	0.6 to 1.4 mmol/kg
Children 4 to 8 years	12.7 kg to 38.9 kg	12.6 mmol	0.32 to 1 mmol/kg
Children 9 to 13 years	21.4 kg to 71.9 kg	26.6 mmol	0.4 to 1.2 mmol/kg
Adolescents 14 to 18 years	36.4 kg to 97.0 kg	22.1 mmol	—
Adults	—	19 to <50 years: 14.7 mmol >51 years: 12.2 mmol	—

Abbreviations: AI = adequate intake; CDC = Centers for Disease Control; IOM = Institute of Medicine; mmol = millimoles; RDA = recommended dietary allowance
There are no functional criteria for phosphorus status that reflect response to dietary intake in infants. Thus recommended intakes of phosphorus are based on AIs that reflect observed mean intakes of infants fed principally with human mi k.
Source: adapted from: https://www.nap.edu/read/5776/chapter/7?term=phosphorus

21 CFR 101 Food Labeling (Nutrition and Supplement Facts)

FDA's labeling regulations for food and dietary supplements include reference daily intakes (RDIs) based on the current RDAs. RDIs include broader age bands than the RDAs. For phosphorus, when the RDI is converted to a weight-base dosage (assuming average bioavailability, as defined above), the resulting value is up to 3 mmol/kg in infants less than 1 year of age.

Table 10. Weight-Based Nutrition and Supplement Facts Labeling

Age Group (CFR defined months/years)	Weight (kg) 5th to 97th Percentile per CDC Growth Charts	RDI in mmol Assuming Average Bioavailability*	Calculated Weight-Based Daily Dosage Assuming Average Bioavailability
Infants birth to 12 months	2.3 kg to 12.6 kg	7 mmol	0.6 to 3 mmol/kg
Children 1 to 3 years	8.3 kg to 17.8 kg	11.6 mmol	0.7 to 1.4 mmol/kg
Children 4 to <12years	12.7 kg to 65.3 kg	32.1 mmol	0.5 to 2.5 mmol/kg
Adolescents**	—	25.7 mmol	—
Adults	—		

* Adults = 63% (midpoint of 55% to 70%); infants/children = 78% (midpoint of 65% to 90%)
** Age group split out separately by reviewer
Abbreviations: CDC = Centers for Disease Control; CFR = Code of Federal Regulations; mmol = millimoles; RDI = reference daily intake
Source: Adapted from Page 242 of 259 of 21 CFR 101 Proposed Revisions to the Nutrition and Supplement Facts Labels (Federal Register Vol 81. No. 103, May 27, 2016)

8.1.2.3. Clinical practice guidelines

Per the ASPEN 2019 Appropriate Dosing for Parenteral Nutrition Guidelines, the recommended daily dosage of phosphorus in PN for adults is 20 to 40 mmol. For adolescents and children weighing more than 50 kg, the recommended daily dosage is 10 to 40 mmol.

No literature data were identified in pediatric patients 12 to <18 years to support ASPEN's recommended daily dosage. The review team determined that pediatric patients 12 years to <18 years should have the same phosphorus requirements as adults and, therefore, the same recommended dosage. These dosage recommendations for patients 12 years to <18 years of age and older are in alignment with current clinical experience and guidelines (Greene et al. 1988; Mirtallo et al. 2004; McClave et al. 2016; Mihatsch et al. 2018; American Society for Parenteral and Enteral Nutrition (ASPEN) 2019). As in adults, requirements in children may be higher or lower depending on individual needs.

ASPEN also provides weight-based dosing recommendations for pediatric population less than 12 years of age (0.5 mmol/kg/day to 2 mmol/kg/day). The ASPEN recommendations are similar to the approved phosphorus dosing in PN for Sodium Phosphates Injection, USP in infants, as shown in the table below.

Table 11. Weight-Based ASPEN Dosing Recommendations

Age Group (FDA-defined age in months/years)	Weight (kg) 5th to 97th Percentile per CDC Growth Charts	Weight-Based Daily Dose	Calculated Total Dose
Preterm neonates birth to 28 days	0.5 kg* to 4.7 kg	1 to 2 mmol/kg	0.5 to 9.4 mmol
Infants 29 days to <2 years	3.2 kg to 15.6 kg	0.5 to 2 mmol/kg	1.6 to 31.2 mmol
Children 2 to <12 years	29.2 kg to 50 kg **	0.5 to 2 mmol/kg	14.6 to 100 mmol
Adolescents 12 to <18 years	>50 kg**	—	10 to 40 mmol
Adults	—	—	20 to 40 mmol

Abbreviations: CDC = Centers for Disease Control; FDA = Food and Drug Administration; mmol = millimoles
* Very low birth weight infants
** Up to 50 kg; ASPEN dosing for children >50 kg is the same as adolescents
Source: ASPEN guidelines 2019

Other clinical guidelines (Greene et al. 1988) also acknowledge that a relatively high phosphorus content in PN is necessary in early infancy (preterm and term infants). As shown in Table 12 below, the estimated weight-based dose for preterm and term infants is similar to ASPEN and to the approved Sodium Phosphates Injection, USP dosing (i.e., up to 2 mmol/kg/day).

Table 12. Weight-Based Dose for Preterm and Term Infants

	Preterm Infant and Term Infants*	Children >1 year*
Phosphorus (per L)	400 to 450 mg/L	150 to 300 mg/L
Calculated dose based on 31 mg =1 mmol	12.9 to 14.5 mmol/L	4.8 to 9.7 mmol/L
Estimated Weight	0.5 to 5 kg	8.3 kg to 17.8 kg (1 to 3 years)
Estimated Weight-Based Dose (per L)	2.6 to 29 mmol/kg/L	0.3 to 1.2 mmol/kg/L
Calculated Average PN Fluid 150 mL/kg/day	75 to 450 mL/day	1 L
Estimated Weight-Based Dose per PN Fluid	1.1 to 2 mmol/kg/day	0.3 to 1.2 mmol/kg

*requirements are less with advancing age; few data available
Abbreviations: mmol = millimoles; PN = parenteral nutrition
Source: Adapted from Greene HL, Hambidge M, Schanler, 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 Nutr 1988;48:1324-42.

8.1.2.4. Published literature

Adults

As noted above, the recommended dosage of phosphorus to maintain normal serum phosphorus levels in adults described in the label for the LD Sodium Phosphates Injection, USP is based upon the amount of dextrose (calories) that the patient is receiving in PN (i.e., 12 to 15 mmol of phosphorus per 250 g dextrose). Grams of dextrose can be converted to calories (1 gram of dextrose =3.4 calories; and 250 g dextrose =850 calories). Therefore, there are 14 to 18 mmol phosphorus/1000 calories. Assuming a typical adult diet of 2500 calories, the corresponding phosphorus dose would be 35 to 45 mmol/day. This phosphorus dose approximates the dosage range of 20 to 40 mmol/day recommended by ASPEN for adults. This dose is also consistent with the RDA/RDI in adults, as described above.

The two available literature studies also support a dose of approximately 14 to 17 mmol of phosphorus/1000 calories in PN to meet daily dietary requirements and prevent hypophosphatemia in adults. Sheldon and Grzyb (1975) report that to maintain normal serum phosphorus levels in patients receiving PN, "Provision of 20 to 25 mEq of potassium dihydrogen phosphate per 1,000 K Calories [1 mmol of phosphate =1.5 mEq of potassium; therefore, 14 to 17 mmol/1000 calories] will maintain normal serum levels of inorganic phosphate during total parenteral nutrition."

Pigon et al. (1985) randomized ICU patients requiring PN to a low phosphorus group and a high phosphorus group. The low phosphorus group received 7.5 mmol from the phospholipids in the fat emulsion and the high phosphorus group received additional supplementation with 60 to 80 mmol/day. With a dose of 80 mmol/day, a positive phosphorus balance was achieved. The authors conclude that 20 to 40 mmol/day may be sufficient for most patients, but that ICU patients may require, and can tolerate, up to 80 mmol/day.

Pediatric Patients

No clinical trials in pediatric patients were found in the literature search. The search conducted by DEPI found "very limited information" in children.

There are two publications describing administration of phosphorus in PN (approximately 2 mmol/kg/day, consistent with ASPEN recommendations) to term and preterm infants; one study was retrospective (Mulla et al. 2017) and one study was prospective (Moltu et al. 2013).

Three other studies (Ichikawa et al. 2012; Ross et al. 2013; Brener Dik et al. 2015) describe the prevalence and the definition of hypophosphatemia in infants receiving PN in addition to enteral nutrition. The amount of phosphorus administered to these patients was less than the ASPEN-recommended dosage of 2 mmol/kg/day. The definition of hypophosphatemia varied by age group. Mild to moderate hypophosphatemia was defined as a serum phosphorus of 3.8 to 4 mg/dL and severe hypophosphatemia as 2.5 mg/dL to 1 mg/dL.

- Ross et al. (2013) reported 41% of very low birth weight (VLBW) infants were found to have mild to moderate hypophosphatemia and 11% of VLBW infants had severe hypophosphatemia.
- Brener Dik et al. (2015) reported 91% of VLBW infants had moderate hypophosphatemia and 34% VLBW infants had severe hypophosphatemia.
- Ichikawa (2012) reported 24% of extra-low birth weight (ELBW) infants had hypophosphatemia.

There are several reasons why preterm and term infants may require higher amounts of phosphorus than older pediatric patients:

- Preterm infants have “low reserves” of phosphorus at baseline. In contrast, hypophosphatemia in critically ill older pediatric patients is generally a result of intracellular shifts of electrolytes, with the exception of malnourished children, where the etiology includes low phosphorus reserves as well. In preterm infants, the low phosphorus reserves are in part attributable to the lack of maternal transfer of calcium and phosphorus that should have occurred during the third trimester of pregnancy, because of the premature delivery. Therefore, preterm infants have a phosphorus deficit at birth. The degree of the phosphorus deficit depends on how premature the infant was and other risk factors such as birth weight, gestational age, intrauterine growth restriction, etc.
- The calcium and phosphorus requirements of preterm infants are higher because of increased growth velocity after birth plus the requirement for catch-up growth. Preterm infants are dependent on PN for macro- and micronutrients, until the infant can be transitioned to enteral feeding and tolerate full enteral feedings.

8.1.2.5. Efficacy summary

The above information from various sources, including daily requirements, clinical guidelines, and clinical studies, supports dosing of Potassium Phosphates Injection, USP in patients from birth to adulthood for the correction of hypophosphatemia in intravenous fluids and for use in PN.

A dosage range of 0.16 mmol/kg to 0.64 mmol/kg as an initial or single dose is recommended for the correction of hypophosphatemia in most patients. The recommended dosage within the dosage range is dependent upon the patients’ baseline serum phosphorus concentration. Adults and pediatric patients less than 1 year of age have different cut-off values for the lower end of the reference range, which defines hypophosphatemia. Based upon clinical requirements, some patients may require a lower or higher dose. The recommended maximum initial or single dose is phosphorus 45 mmol (potassium 66 mEq). Additional dose(s) following the initial dose may be needed in some patients. There is no maximum daily dosage, and serum phosphorus levels are used to assess the patients’ repletion status.

(b) (4)

hyperphosphatemia occurred with the higher doses of intravenous potassium phosphates in the publications reviewed (e.g., 1 mmol/kg and higher). See Section 8.2.4.4 Hyperphosphatemia.

For use in PN, the recommended phosphorus dosage in adults and pediatric patients 12 years of age and older is 20 mmol to 40 mmol/day. The recommended phosphorus dosage in pediatric patients 1 year to <12 years of age is 1 mmol/kg/day to a maximum of 40 mmol, to align with the recommended dosage in adults and pediatric patients 12 years of age and older.

A relatively higher dosage of 2 mmol/kg/day is recommended in pediatric patients from birth (including preterm and term infants) to 1 year of age to meet dietary needs.

The dosage should be individualized 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 PN may be limited by the amount of calcium that is also added to the solution. Serum phosphorus, potassium, calcium, and magnesium concentrations should be monitored during treatment.

8.2. Review of the Safety Database

The safety review for intravenous potassium phosphates is based on the LDs, literature including clinical trials, guidelines and clinical practice, and postmarketing pharmacovigilance reports.

8.2.1. Listed Drugs

The Applicant is relying on the summary findings of safety (and effectiveness) of Sodium Phosphates Injection, USP (NDA 018892). The labeling for this product describes the risks of hyperphosphatemia and hypocalcemia associated with the active moiety, phosphorus.

The labeling of Potassium Chloride Injection (NDA 020161) is cited as a source of safety information about the potassium ion. Specifically:

> *… the recommended administration rate should not usually exceed 10 mEq/hour or 200 mEq for a 24-hour period if the serum potassium level is greater than 2.5 mEq/liter.*

In urgent cases where the serum potassium level is less than 2 mEq/liter or where severe hypokalemia is a threat (serum potassium level less than 2 mEq/liter and electrocardiographic changes and/or muscle paralysis), rates up to 40 mEq/hour or 400 mEq over a 24-hour period can be administered very carefully when guided by continuous monitoring of the ECG and frequent serum K^+ determinations to avoid hyperkalemia and cardiac arrest.

8.2.2. Guidelines and Clinical Experience

Current practice guidelines, which are supported by clinical experience and the published literature, support the safety of phosphorus at the recommended dosage for the correction of hypophosphatemia in intravenous fluids and for use in PN in adult and pediatric patients (Greene et al. 1988; Mirtallo et al. 2004; Mihatsch et al. 2018; American Society for Parenteral and Enteral Nutrition (ASPEN) 2019).

8.2.3. Adverse Events in Published Clinical Studies

The clinical studies that were reviewed for efficacy were also reviewed for safety. See Table 5, Table 6, Table 7, and Table 8. Most of the safety information was obtained from adults who received intravenous sodium or potassium phosphates for the correction of hypophosphatemia.

Safety information was obtained from:

- Thirteen clinical studies in adult patients for the treatment of hypophosphatemia, which include a total of 526 adults and 511 who received intravenous potassium phosphates:
  - Eight U.S. studies (Vannatta et al. 1981; Wilson et al. 1982; Vannatta et al. 1983; Andress et al. 1984; Clark et al. 1995; Rosen et al. 1995; Taylor et al. 2004; Brown et al. 2006)
  - Five non-U.S. studies (Kingston and Al-Siba'i 1985; Pigon et al. 1985; Perreault et al. 1997; Charron et al. 2003; Bech et al. 2013)
- One study in pediatric patients for the treatment of hypophosphatemia (Leite et al. 2017)
- Four studies in patients who received phosphorus in PN:
  - Two adult studies (Sheldon and Grzyb 1975; Pigon et al. 1985)
  - Two studies in preterm and term infants (Moltu et al. 2013; Ross et al. 2013; Mulla et al. 2017)

Other literature describing serious ARs with intravenous sodium and/or potassium phosphates is shown in Table 13 below.

Table 13. Relevant Studies Related to Serious Adverse Reactions With Intravenous Sodium or Potassium Phosphates – Summary Prepared by DEPI

Shackney (1967) reports two cases of hypotension and renal failure leading to death in patients treated with 50 to 100 mmol P IV for high calcium.
After observing one case of symptomatic hypocalcemia with hyperphosphatemia, Zipf (1979) prospectively assesses seven children (age 9 to 17 years) with diabetic ketoacidosis managed with potassium phosphate IV.
Winter (1979) describes one case of hypomagnesemia, hypocalcemia, and hyperphosphatemia attributed to potassium phosphates IV in a 9-year-old boy with diabetic ketoacidosis.
Chernow (1981) describes symptomatic hypocalcemia during treatment with potassium phosphate IV in a 50-year-old man with diabetic ketoacidosis and in a 66-year-old alcoholic woman with hypophosphatemia.
Wetherton (2003) presents four cases of in-hospital death associated with accidental intravenous administration of potassium chloride (N=3) or potassium phosphate (N=1, 26.4 mmol push, age 81 years).
Felton (2006) describes clinical deterioration in a 43-year-old septic patient 90 minutes after the sequential intravenous administration of calcium gluconate and potassium phosphates.

Abbreviations: DEPI = Division of Epidemiology; IV = intravenous; mmol = millimoles; NDA = new drug application
Source: Table 7 from DEPI review by Joel Weissfeld

Intravenous potassium phosphates are contraindicated in patients with hyperkalemia; hyperphosphatemia; hypercalcemia or significant hypocalcemia; or severe renal impairment (eGFR less than 30 mL/min/1.73 m^2) or ESRD. Most studies in adults excluded patients with renal impairment and other comorbidities, except for the studies by Perreault et al. (1997) and Kingston and Al-Siba'I (1985).

Hyperphosphatemia occurred with the higher doses of intravenous potassium phosphates in adults the publications reviewed (e.g., 1 mmol/kg).

Hyperkalemia was also reported in several of the publications reviewed with administration of potassium phosphates in adults. In general, use of potassium phosphates should be limited to

patients with a serum potassium level of <4 mEq/dL at baseline to minimize the potential risk for hyperkalemia. Sodium phosphates injection can be used as an alternative in patients with serum potassium ≥4 mEq/dL.

Hypocalcemia was also reported in a few of the adult published clinical trials, but only one occurrence of symptomatic hypocalcemia was reported (Chernow et al. 1981).

Hypomagnesemia was also reported in association with hypophosphatemia.

AEs reported in pediatric patients were similar to those reported in adults (i.e., primarily electrolyte disturbances).

8.2.4. Specific Safety Issues

8.2.4.1. Hyperkalemia

Normal potassium levels in the blood range from 3.5 to 5.0 mEq/L. Potassium levels between 5.1 mEq/L to 6.0 mEq/L are defined as mild hyperkalemia.

It is well established that rapid or bolus infusion of potassium-containing products can cause significant morbidity and potential mortality because of hyperkalemia. Hyperkalemia can develop with overzealous administration of injectable potassium or secondary to impaired potassium excretion (acute/chronic kidney injury, adrenal insufficiency, etc.). Severe hyperkalemia can cause muscle weakness, heart palpitations, and sometimes, life- threatening cardiac arrythmias (Maxwell et al. 2013). Peaked T waves are generally the earliest sign of hyperkalemia; however, it can also present with QRS widening, conduction block, ventricular fibrillation, asystole, etc. (Diercks et al. 2004).

Therefore, while the active ingredient is phosphate, administration of potassium phosphates must also take into consideration the dose of potassium being co-administered. The patient's baseline serum potassium level, degree of renal impairment, and concomitant medications with the potential to increase potassium should also be considered. In general, patients with a baseline serum potassium of >4 mEq/dL should not be treated with potassium phosphates products and should instead receive a sodium phosphates product because of the increased risk for treatment-related hyperkalemia (Hemstreet et al. 2006) in such patients. Patients with severe renal impairment and ESRD also should not receive the potassium phosphates product due to their inability to excrete excess phosphorus and disruption of phosphorus homeostasis. Patients with moderate renal impairment should be treated cautiously and receive a dosage at the lower end of the dosing range.

Other patients at increased risk of hyperkalemia include those with severe adrenal insufficiency or treated concurrently with other drugs (e.g., digoxin) that cause or increase the risk of hyperkalemia. Patients with cardiac disease may be more susceptible to the effects of hyperkalemia.

Maximum Amount of Potassium

The recommended initial, or single, dose noted in the labeling for the indication 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 is phosphorus 0.64 mmol/kg (potassium 0.94 mmol/kg). Weight should be in terms of actual body weight. Limited information is available regarding dosing of patients significantly above ideal body weight; therefore, an adjusted body weight may be used for these patients. The maximum single dose is 45 mmol/dose of phosphorus (66 mEq mEq/kg of potassium). Subsequent doses may be given, as needed, based on the patient's response. In adults, the MDD of potassium chloride reported in the literature to correct hypokalemia is approximately 200 to 400 mEq/day (Kruse and Carlson 1990). The potassium content of other products must also be taken into consideration in the calculation of total daily dose and the maximum age-adjusted daily dose for potassium should not be exceeded.

For infants and children, the maximum dose is contingent on the potassium dose and maximum fluid volume that can be administered. For both neonates and children, the amount of fluid that can be administered and restrictions relating to the potassium dose will limit the amount of phosphorus administered in a day.

Table 14. Relevant Studies Related to Potassium

Author Year	Summary
Singhi (1994)	Administered concentrated potassium chloride (200 mmol/L [200mEq/L]) at 0.25 mmol/kg/hour to 20 hypokalemic children.
Kruse and Carlson (1990)	Studied potassium infusion in ICU and recommended 20mEq/100cc/hour for correction of hypokalemia
Kruse (1994)	Assessed 40 ICU patients administered potassium chloride 20 mmol (20 mEq) IV over a 1-hour period.

Abbreviations: ICU = intensive care unit; IV = intravenous; mEq = milliequivalents; mmol = millimoles
Source: Reviewer table

8.2.4.2. Pulmonary embolism secondary to pulmonary vascular precipitates

See the review by DEPI filed under NDA 020678 and 020734, July 2, 2013, regarding risk of pulmonary vascular precipitates associated with PN and additives. The language in the labeling for this Warning and Precaution is standard language for products administered with PN and reflects the results of a thorough review of this topic by DEPI.

There will also be a contraindication in labeling against use in patients with hypercalcemia to reduce the risk of calcium-phosphate precipitation.

Potassium Phosphates Injection, USP, when administered in intravenous fluids for the correction of hypophosphatemia, should not be infused with calcium-containing intravenous fluids. When admixed in PN, the calcium and phosphate ratios of the final solution must be considered. Calcium-phosphate stability in PN solutions is dependent upon the pH of the solution, temperature, and relative concentration of each ion.

8.2.4.3. Serious cardiac adverse reactions with undiluted, or bolus or rapid intravenous administration

AEs have been reported in the literature and FDA Adverse Event Reporting System (FAERS) with unapproved marketed formulations of potassium phosphates and approved sodium phosphates when administered inappropriately (i.e., without adequate dilution and/or when infused rapidly). Serious AEs include cardiac arrhythmia (including QT prolongation), cardiac arrest, seizures, muscle spasms, and death (see 8.2.5 Pharmacovigilance).

Therefore, Potassium Phosphates Injection, USP must be diluted in appropriate amounts of intravenous fluid or PN (see 8.2.4.9 Vein Damage and Phlebitis) and administered at no more than the maximum rate indicated in the labeling.

Maximum Infusion Rate

The maximum infusion rate of Potassium Phosphates Injection, USP is limited by the amount of potassium and phosphorus in the solution and the concentration of the solution.

For correction of hypophosphatemia, the maximum recommended infusion rate in adults via a peripheral line should generally not exceed 6.8 mmol/hour of phosphorus (10 mEq/hour of potassium). This recommendation is based upon extensive clinical experience and general practice guidelines, based on scientific literature, for the administration of potassium.

In adults and adolescents with severe hypophosphatemia, up to 15 mmol/hour of phosphorus (23.5 mEq/hour of potassium) can be administered in a central line in the setting of continuous ECG monitoring and monitoring of serum potassium concentrations. Higher doses and/or faster infusion rates are associated with adverse effects including electrolyte disturbances and end-organ dysfunction (Shackney and Hasson 1967).

Various guidelines and institutions have standardized potassium infusion rates for neonates (Daly and Farrington 2013; Rhodes et al. 2016). The potassium infusion that can be administered in neonates and infants is 0.5 to 1 mEq/Kg intravenously over 1 hour; the patient should then be reassessed.

In pediatric patients weighing up to 20 kg, an infusion rate of more than 3.2 mmol/kg/hour of phosphorus (0.5 mEq/kg/hour potassium) should be accompanied by continuous cardiac monitoring. This recommendation is supported by current clinical experience and practice guidelines (Greene et al. 1988; Koletzko et al. 2005; SickKids Nutrition Team 2007; Mihatsch et al. 2018).

8.2.4.4. Hyperphosphatemia

Iatrogenic hyperphosphatemia can develop with overzealous administration of injectable phosphate. Clinically significant iatrogenic hyperphosphatemia was diagnosed in an adult hospitalized for diabetic ketoacidosis (DKA) and another admitted for chronic alcoholism and pneumonia after administration of intravenous potassium phosphates. The AEs described in

these case reports were associated with very large infusions of potassium phosphates daily (approximately 115 to 170 mmol phosphate per day, which is higher than the recommended maximum dosage for a single or initial dose in the PI for Potassium Phosphates Injection, USP); however, it is important to note that these patients never exhibited hyperkalemia (Shackney and Hasson 1967; Winter et al. 1979; Chernow et al. 1981).

8.2.4.5. Hypocalcemia

Potassium Phosphates Injection, USP should be used with caution in patients with hypocalcemia due to an increased risk for worsening hypocalcemia. While injection of phosphates can cause hypocalcemia, there are few published reports of clinically significant hypocalcemia when appropriate doses are used. However, clinically significant hypocalcemia has occurred at higher doses secondary to impaired synthesis of the active form of vitamin D, decreased urinary calcium excretion, and increased bone resorption, leading to an imbalanced calcium to phosphorus ratio (Shackney and Hasson 1967; Winter et al. 1979; Chernow et al. 1981). Hypocalcemia can induce prolongation of the QT interval with subsequent development of arrhythmias, muscle spasms, etc. In general, serum calcium levels should be corrected prior to administration of Potassium Phosphates Injection, USP. This recommendation is supported by the known physiology, the reviewed literature, and the current clinical experience and practice guidelines derived from the literature (Shackney and Hasson 1967; Greene et al. 1988; Mirtallo et al. 2004; Hemstreet et al. 2006; McClave et al. 2016; Mihatsch et al. 2018; American Society for Parenteral and Enteral Nutrition (ASPEN) 2019).

8.2.4.6. Hypercalcemia

Intravenous potassium phosphates are contraindicated in patients with hypercalcemia due to the increased risk of formation of insoluble calcium phosphorus precipitates in these patients. This recommendation is supported by the known physiology, the reviewed literature and the current clinical experience and practice guidelines (Shackney and Hasson 1967; Greene et al. 1988; Mirtallo et al. 2004; Hemstreet et al. 2006; McClave et al. 2016; Mihatsch et al. 2018; American Society for Parenteral and Enteral Nutrition (ASPEN) 2019).

8.2.4.7. Hypomagnesemia

DPV-I completed a review evaluating the literature for an association between hypomagnesemia and Potassium Phosphates Injection, USP (dated September 11, 2019). DPV-I's search of PubMed, Embase, and Web of Science through August 5, 2019 identified three publications of interest; one publication described the use of IV potassium phosphate to treat hypercalcemia of malignancy in adults (Fulmer et al. 1972), and two publications described the use of IV potassium phosphate for the treatment of DKA in children (Winter et al. 1979; Zipf et al. 1979).

These uncontrolled case series and reports suggest that systemic acute administration of potassium phosphate may be associated with a decline in serum magnesium levels. Although the case series in hypercalcemic cancer patients could be considered obsolete information

because phosphate salts are no longer recommended for management of hypercalcemia, potassium phosphate continues to be used in the management of DKA and, therefore, the reports addressing this condition are relevant to current practice.

Additionally, the publications contained a limited number of patients and, in some cases, limited information about the administered dose of phosphate and/or incomplete record of the electrolyte levels prior to and after administration of potassium phosphate. The available evidence, however, suggests the possibility that certain patients receiving potassium phosphate infusion may experience a decline in magnesium levels if: (1) the product is infused too rapidly or in excessive amount, thus causing calcium-phosphorus products that exceed approximately 55 mg^2/dL^2, (2) the product is infused as part of treatment of DKA, and (3) the product is infused in children during their rapid growth phase.

8.2.4.8. Aluminum content of drug product

To limit the risk of aluminum toxicity with Potassium Phosphates Injection, USP, the regulatory language found in regulations on "Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition" (21 CFR 201.323) and enacted in the Final Rule in July 2004 (65 FR 4103) was added to the labeling. The Final Rule requires that SVP products must state the maximum aluminum concentration at the time of product expiry on the product's label and provide in the PI a standardized warning describing the presence of aluminum in the product, the risk of using the products in infants and patients with impaired kidney function, and a recommended maximum daily aluminum exposure of 4 to 5 mcg/kg/day (21 CFR 201.323).

Per toxicology review, the Applicant's maximum aluminum content/specification is justified. At these doses and maximum aluminum content, the aluminum exposure does not exceed 5 mcg/kg/day for the indicated population per guidelines in 21 CFR 201.323.

Additionally, per the Applicant, the proposed product's maximum aluminum content is lower than the recently approved Potassium Phosphates Injection, USP product (NDA 212121), and the unapproved products currently on the market.

8.2.4.9. Vein damage and phlebitis

Intravenous administration of concentrated potassium solutions is known to cause venous thrombophlebitis. The labeling for Potassium Chloride Injection (NDA 020161) cites 300 to 400 mEq/L as the maximum concertation that should be administered by the central route.

Pediatric guidelines and publications propose maximum concentrations of potassium 40 mEq/L for peripheral and 80 mEq/L for central venous infusions. This recommendation is based upon extensive clinical experience and general practice guidelines based on scientific literature, for the administration of potassium (University Health System ; Alabsi 2011; Ypeda 2014).

In adults and pediatric patients 12 years of age and older, a total volume of 100 mL or 250 mL is recommended for Potassium Phosphates Injection, USP when prepared in intravenous fluids. The maximum concentration should not exceed phosphorus 6.8 mmol/100 mL (potassium 10

mEq/100 mL) when infused peripherally and 18 mmol/100 mL (potassium 26.4 mEq/100 mL) when infused centrally.

For pediatric patients less than 12 years of age, the smallest volume is recommended, considering the maximum concentration for peripheral and central administration as described for older pediatric patients and adults.

For PN, the maximum concentration infused peripherally is determined by the osmolarity of the final admixed solution. PN solutions with an osmolarity of 900 mOsm/L or greater must be infused through a central venous catheter. Higher rates can cause chemical phlebitis, as reported in the FAERS database and adverse event reported by the Applicant.

8.2.5. Postmarketing Experience

DPV-I completed a review, dated September 13, 2019, of all reports of adverse events associated with IV administration of Potassium Phosphates Injection, USP or Sodium Phosphates Injection, USP (i.e., the LD for this NDA) in the FAERS database through April 22, 2019.

The search of the FAERS database identified 15 AE cases with IV potassium phosphates and no cases with sodium phosphates injection; of these 15 cases, 14 involved improper IV administration of Potassium Phosphates Injection, USP and one involved usual use. The 14 cases involving improper administration of Potassium Phosphates Injection, USP described patients who received rapid IV administration of potassium phosphates (n=6), precipitated calcium/potassium phosphates admixtures (n=4), potassium phosphates overdosage (n=3), or potassium phosphates by an unspecified incorrect route of administration (n=1). The remaining case described acute phosphate nephropathy with renal biopsy-confirmed renal tubular deposition of calcium-phosphorus products (i.e., nephrocalcinosis) with a probable causal association with usual use of IV potassium phosphates.

Of the six cases 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, USP (doses ranged from 15 mmol phosphates/22 mEq potassium to 45 mmol phosphates/66 mEq potassium), and one described a patient who received 30 mmol phosphates/44 mEq potassium intravenously over 1 hour. Some cases of “IV push” administration reported that the undiluted product was present in a patient care area or at the patient’s bedside (n=4) or was accidentally administered due to confusion of Potassium Phosphates Injection, USP with a heparin flush (n=2). These six cases encompassed the following terms included in the proposed ADVERSE REACTIONS section in association with IV potassium phosphates administration at a rate faster than recommended in DOSAGE AND ADMINISTRATION: cardiac arrhythmia, hyperkalemia, hyperphosphatemia, hypocalcemic tetany, and hypotension. Furthermore, these six cases described the following AEs with combined potassium and phosphate intoxication that were not included in the proposed ADVERSE REACTIONS section: bradycardia and cardiac arrest. These terms have been added to this section of labeling.

Of the four FAERS cases that involved IV administration of precipitated calcium/potassium phosphates admixture, three had an outcome of death. These cases involved inappropriate, concomitant administration in the same IV bag of incompatible concentrations of calcium- and phosphate-containing products, resulting in precipitation of product aggregates. The Applicant's proposed DRUG INTERACTIONS section of the labeling (b) (4) These four cases describe the events cardiac arrest and dyspnea following IV administration of precipitated calcium/potassium phosphates admixture. (b) (4) WARNINGS AND PRECAUTIONS (5.2) has been updated to reflect that fatal cases of pulmonary embolism resulting from calcium/phosphate precipitates have occurred.

Of three FAERS cases of IV potassium phosphates overdosage, two had an outcome of death. These cases described patients who received IV potassium phosphates overdosages in the following manners: two adult patients; one of whom had received approximately 100 mmol phosphates/94 mEq potassium (including both sodium and potassium phosphates) in PN over an unreported duration of time, and one who had received 273 mmol phosphates/400 mEq potassium over 3 hours and died; and one infant who had received 17.4 mmol phosphates/25.5 mEq potassium over an unreported duration and died. These cases encompassed the following terms included in the proposed OVERDOSAGE section of the labeling: cardiac arrest, cardiac arrhythmia, hyperkalemia, hyperphosphatemia, tetany, (b) (4) Furthermore, the FAERS case series described bradycardia and hypotension following IV potassium phosphates overdosage.

8.2.5.1. Expectations on safety in postmarket setting

Secondary to reports of inappropriate administration and medication errors, in 2006, an Institute of Safe Medicine Practice newsletter was published regarding safe handling of concentrated electrolyte products from outsourcing facilities during critical drug shortages (Institute for Safe Medication Practices 2018b).

On April 18, 1994, FDA published a safety alert that it had received a report from an institution of two deaths and at least two cases of respiratory distress developed during peripheral infusion of a PN mixture. The solution may have contained a precipitate of calcium phosphate. Autopsies revealed diffuse microvascular pulmonary emboli containing calcium phosphate. One literature report cites an adult case of subacute interstitial pneumonitis associated with calcium phosphate precipitates. FDA suggested steps in preparing PN to decrease these risks (Lumpkin 1994).

A 2013 article "Reducing the risk of harm from intravenous potassium: A multifactorial approach in the haematology setting," and consensus guidelines from other regulatory agencies emphasized the need for concentrated electrolyte solutions to be stored and prepared only in

the hospital pharmacy and not in patient-care areas (Barras et al. 2014; Institute for Safe Medication Practices 2018a; The Joint Commission 2019).

No new safety concerns are expected in the postmarket setting with this potassium phosphates product and the previously unapproved marketed products.

8.2.6. Safety Analyses by Demographic Subgroups

8.2.6.1. Patients with renal impairment

Use of Potassium Phosphates Injection, USP in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) or ESRD is contraindicated due to both the risk for hyperphosphatemia and hyperkalemia. When administering potassium phosphates in patients with moderate renal impairment (eGFR >30 and <60 mL/min/1.73 m^2), a cautious approach including starting at the lower end of the dosage range is recommended. More frequent monitoring should also be considered. These recommendations are supported by the known mechanism of action and physiology of potassium phosphates products as well as current clinical experience and practice guidelines (Greene et al. 1988; Locatelli et al. 2002; Mirtallo et al. 2004; McClave et al. 2016; Mihatsch et al. 2018; American Society for Parenteral and Enteral Nutrition (ASPEN) 2019). No change in dosing is described in labeling for patients with mild renal impairment.

8.2.6.2. Geriatric patients

Since geriatric patients frequently have decreased renal function, caution is advised in dosing and starting at the lower end of the dosage range is recommended, in addition to monitoring of renal function.

8.2.7. Specific Safety Studies/Clinical Trials

8.2.7.1. QT assessment

See the CDER Division of Cardiovascular and Renal Products QT Interdisciplinary Review Team memorandum by Christine Garnett, Pharm.D., Clinical Analyst, filed in DARRTS by Nan Zheng, August 8, 2019.

The Division of Cardiovascular and Renal Products QT review stated that, “A TQT study is not needed per ICH E14 because the doses for potassium and phosphate are not substantially higher than approved products on U.S. market.”

8.2.8. Human Reproduction and Pregnancy

The Division of Pediatric and Maternal Health (DPMH) was consulted to assist with evaluating the safety of Potassium Phosphates Injection, USP in pregnancy and lactation. Refer to the DPMH Maternal Health Labeling Review dated, September 4, 2019, (Kristie Baisden, DO and Tamara Johnson, MD, MS) for additional details.

Briefly, DPMH did not identify any relevant published literature related to the use of intravenous potassium phosphates in pregnancy, lactation, or effects on fertility. However, DPMH notes that phosphorus is an essential mineral element needed for numerous metabolic functions. Although animal reproduction studies have not been conducted with Potassium Phosphates Injection, USP, both potassium phosphates and the LD relied upon (sodium phosphates) have been used in humans for decades. As there are no published reports of adverse outcomes due to phosphate supplementation in pregnant or lactating women, DPMH concluded that administration of the approved recommended dose of Potassium Phosphates Injection, USP is not expected to be harmful during pregnancy or lactation.

8.2.9. Integrated Assessment of Safety

The safety of phosphorus in Potassium Phosphates Injection, USP is based the findings of safety (and effectiveness) for Sodium Phosphates Injection, USP (NDA 18-892) and upon published literature including clinical trials, primarily in adult patients, with, or at risk for, hypophosphatemia, guidelines and clinical practice, and postmarketing pharmacovigilance reports. The safety of the potassium salt is based upon the and findings of safety for Potassium Chloride Injection (NDA 020161) and published literature.

While acknowledging the limitations with the collection and description of AEs in the published studies, there has been considerable postmarketing experience with both intravenous potassium phosphates and sodium phosphates in patients of all ages. Serious ARs associated with intravenous administration of potassium phosphates include hyperkalemia, hyperphosphatemia, hypocalcemia, and hypomagnesemia. Several published case reports have documented serious adverse outcomes when intravenous phosphorus in intravenous fluids is administered to adults in single doses of 50 mmol or more over 3 hours or less for the correction of hypophosphatemia. ARs within the recommended dosage range, at the recommended infusion rate, are rarely clinically significant.

Solutions that contain potassium ions should be used with great care, if at all, in patients with hyperkalemia, severe renal failure, and in conditions in which potassium retention is present. In patients with diminished renal function, administration of solutions containing potassium ions may result in potassium retention. Therefore, Potassium Phosphates Injection, USP is contraindicated in patients with hyperkalemia; hyperphosphatemia; hypercalcemia or significant hypocalcemia; or severe renal impairment (eGFR less than 30 mL/min/1.73 m^2) or ESRD. To minimize the risk of hyperkalemia, when administering potassium phosphates for the correction of hypophosphatemia, the baseline serum potassium level should be assessed and Potassium Phosphates injection, USP should not be administered to patients with serum potassium levels of 4 mEq/dL or higher, and an alternative source of phosphorus should be considered.

It is also important to normalize serum calcium levels prior to infusion of phosphates. Infusing high concentrations of phosphorus may cause hypocalcemia. If significant hypocalcemia is present, infusion of phosphorus can cause severe hypocalcemia with tetany. If phosphorus is infused in the setting of hypercalcemia, it can lead to the formation of precipitates. Serum

magnesium is also frequently low in hypophosphatemic patients and may decrease, especially with rapid infusion, and should also be normalized prior to treatment.

Administered incorrectly (i.e., higher than recommended dosages, inadequate dilution, and/or rapid infusion), serious cardiac Ars, including death, have occurred with intravenous potassium phosphates. However, when the recommended dosage is diluted and administered at the appropriate rate with appropriate monitoring, the potassium content of this product is safe. Therefore, Potassium Phosphates Injection, USP is to be used for intravenous infusion only after dilution or admixing and administered at a rate equal to or less than the maximum recommended rate, and the patient should be monitored appropriately with continuous electrocardiographic monitoring, as needed.

The risk of hyperkalemia is increased in patients with severe adrenal insufficiency or treated concurrently with other drugs that cause or increase the risk. Patients with cardiac disease may be more susceptible to the effects of hyperkalemia. Consider the amount of potassium from all sources when determining the dose of Potassium Phosphates Injection, USP and do not exceed the maximum age-appropriate recommended daily amount of potassium. In patients with moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2), start at the low end of the dose range. Close monitoring of serum phosphorus, calcium, magnesium and potassium, along with other serum electrolytes, are necessary prior to, during, and after treatment.

8.3. Statistical Issues

Not applicable.

8.4. Conclusions and Recommendations

The literature submitted, and the additional literature reviewed, along with FDA's findings of safety and efficacy for the LDs, support the efficacy and safety of Potassium Phosphates Injection, USP for the indications of:

8.4.1. In Intravenous Fluids to Correct Hypophosphatemia

Potassium Phosphates Injection, USP is indicated as a source of phosphorus in intravenous fluids to correct hypophosphatemia in adults and pediatric patients when oral or enteral replacement is not possible, insufficient, or contraindicated.

8.4.2. For Parenteral Nutrition

Potassium Phosphates Injection, USP is indicated as a source of phosphorus for PN in adults and pediatric patients when oral or enteral nutrition is not possible, insufficient, or contraindicated.

The risk/benefit profile of Potassium Phosphates Injection, USP is similar to the LD Sodium Phosphates Injection, USP, except for the difference in the salt. Potassium phosphates have been used extensively in clinical practice (with unapproved marketed formulations) for many

years and the literature reviewed and current guidelines, derived from the clinical literature, support the recommended dosing regimen. The information and postmarketing pharmacovigilance data also supports the safety and recommended dosing regimen. The Applicant's maximum aluminum content/specification is justified, and the aluminum exposure does not exceed 5 mcg/kg/day for the indicated population per 21 CFR 201.323; therefore, Potassium Phosphates Injection, USP is safe for pediatric patients of all ages (birth to <18 years) and adults.

In conclusion, the benefits of the proposed product outweigh the potential risks, and approval of NDA 212832 for Potassium Phosphates Injection, USP in adults and pediatric patients for the two proposed indications is recommended.

9. Advisory Committee Meeting and Other External Consultations

This application was not referred to an FDA Advisory Committee as no controversial issues that would benefit from advisory committee discussion were identified.

10. Pediatrics

Under the Pediatric Research Equity Act (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, USP proposes a new dosing regimen (weight-based dosing) for pediatric patients less than 12 years of age, including neonates, and therefore triggers the Pediatric Research Equity Act. However, there is an approved NDA 018892 for Sodium Phosphates Injection, USP by Hospira, LLC that is indicated in all pediatric age groups. NDA 212832 relies on FDA's findings of safety and efficacy for NDA 018892 for Sodium Phosphates Injection, USP, the listed product by Hospira and on FDA's findings of safety for NDA 020161 for Potassium Chloride Injection, the listed product by ICU Medical, Incorporated.

A similar Potassium Phosphates formulation (under NDA 212121 by CMP Development, Inc.) was FDA-approved on September 19, 2019, for adults and pediatric patients 12 years and older. Labeling for NDA 212121 Potassium Phosphates Injection, USP. The Indications and Usage section of that product's labeling states:

> ***In Intravenous Fluids to Correct Hypophosphatemia***
>
> *Potassium Phosphates Injection is 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***
>
> *Potassium Phosphates Injection is indicated as a source of phosphorus for parenteral nutrition (PN) 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 PN 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 [see Warnings and Precautions (5.5), Use in Specific Population (8.4)].

Unlike the CMP product, this potassium phosphates product (under NDA 212823) 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 PN in adults and pediatric patients when oral or enteral nutrition is not possible, insufficient, or contraindicated.

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

There are no adequate and well-controlled clinical studies in pediatric patients. Phosphorus dosing to correct hypophosphatemia and for use in PN requirements in pediatric patients down to neonates are described in clinical practice guidelines for PN formulation recommendations; these guidelines generally rely upon the literature discussed in this review.

The safety risks of hyperkalemia, hyperphosphatemia, and hypocalcemia are similar to adults.

Section 10 (Pediatric Use) will reflect that safety and effectiveness of Potassium Phosphates Injection, USP have been established in pediatric patients from birth to less than 18 years of age for the indication of a source of phosphorus to correct hypophosphatemia, and that safety and effectiveness of Potassium Phosphates Injection, USP have been established for the PN indication in pediatric patients from birth to less than 18 years of age. A separate DPMH Labeling Review for NDA 212832 is in the Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) dated September 4, 2019.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

1. INDICATIONS AND USAGE

As described above, the LD, Sodium Phosphate Injection, USP, has the following indication:

> *[I]s indicated as a source of phosphorus, for addition to large volume intravenous fluids, to prevent or correct hypophosphatemia in patients with restricted or no oral intake. It is also useful as an additive for preparing specific parenteral fluid formulas when the needs of the patient cannot be met by standard electrolyte or nutrient solutions. The concomitant amount of sodium (Na^+ 4 mEq/mL) must be calculated into total electrolyte dose of such prepared solutions.*

To modernize the indication(s) and better describe the indication population(s), the proposed indications statement was revised into two separate indications:

> *Potassium Phosphates Injection is indicated as a source of phosphorus:*
>
> - *In intravenous fluids to correct hypophosphatemia in adults and pediatric patients when oral or enteral replacement is not possible, insufficient, or contraindicated*
> - *For parenteral nutrition in adults and pediatric patients when oral or enteral nutrition is not possible, insufficient, or contraindicated*

FDA's Established Pharmacologic Class text phrase for labeling was proposed as "phosphorus replacement product." The official Established Pharmacologic Class (for posting on eList) will be "parenteral phosphorus replacement."

2. DOSAGE AND ADMINISTRATION

Preparation and Administration

The instructions are provided separately for the two indications (in intravenous fluids and in parenteral nutrition). The following important points are included:

- The product must be diluted or admixed prior to use and is not for direct intravenous injection due to the risk of serious cardiac ARs with infusion of undiluted solution.
- The product is only appropriate for the correction of hypophosphatemia in patients with a baseline serum potassium concentration of less than 4 mEq/dL due to the potassium content.
- Normalize the serum calcium before administering and do not infuse with calcium-containing intravenous fluids. The calcium-phosphate ratio in PN must be considered. These instructions relate to the risk of hypocalcemia and precipitation of calcium phosphate causing pulmonary vascular precipitates.

Dosage

The LD, Sodium Phosphates Injection, USP, has the following information about the need to individualize the dosage, but only includes a specific dosage regimen for one of the indications (admixed in parenteral nutrition):

> *The dose and rate of administration are dependent upon the individual needs of the patient. Serum sodium, phosphorus, and calcium levels should be monitored as a guide to dosage. In patients on total parenteral nutrition, approximately 12 to 15 mmol of phosphorus (equivalent to 372 to 465 mg elemental phosphorus) per liter bottle of PN solution containing 250 g dextrose is usually adequate to maintain normal serum phosphorus, though larger amounts may be required in hypermetabolic states. The amount of sodium and phosphorus which accompanies the addition of sodium phosphate also should be kept in mind, and if necessary, serum sodium levels should be monitored. The suggested dose of phosphorus for infants receiving PN is 1.5 to 2 mmol P/kg/day.*

As described in this review, the dose of phosphorus in intravenous fluids for adults and pediatric patients to correct hypophosphatemia was determined based upon clinical studies in the literature and general understanding of the physiology of phosphorus repletion in adults and pediatric patients. In addition to the phosphorus dose, the corresponding dose of potassium is also included. The dosage is dependent upon the individual needs of the patient, and the contribution of phosphorus and potassium from other sources. The phosphorus doses in the label (shown in Table 15) are general recommendations for an initial or single dose and are intended for most patients. Based upon clinical requirements, some patients may require a lower or higher dose. A maximum recommended initial or single dose is included, due to the risk of serious cardiac ARs reported with single doses above approximately 50 mmol.

Patients may require more than a single dose and treatment over several days to correct hypophosphatemia. Subsequent doses following the initial dose should be adjusted as needed based upon clinical and laboratory parameters.

Table 15. Recommended Initial or Single Dose of Potassium Phosphates Injection in Intravenous Fluids to Correct Hypophosphatemia in Adults and Pediatric Patients

Serum Phosphorus Concentration[a]	***Phosphorus Dosage[b,c]***	***Corresponding Potassium Content***
1.8 mg/dL to lower end of reference range[a]	*0.16 mmol/kg to 0.31 mmol/kg*	*Potassium; 0.23 mEq/kg to 0.46 mEq/kg*
1 mg/dL to 1.7 mg/dL	*0.32 mmol/kg to 0.43 mmol/kg*	*Potassium; 0.47 mEq/kg to 0.63 mEq/kg*
Less than 1 mg/dL	*0.44 mmol/kg to 0.64 mmol/kg*	*Potassium; 0.64 mEq/kg to 0.94 mEq/kg*

[a] Serum phosphorus reported using 2.5 mg/dL as the lower end of the reference range for healthy adults and pediatric patients 12 months of age and older. Serum phosphorus reported using 4 mg/dL as the lower end of the reference range for preterm and term infants less than 12 months of age. Serum phosphorus concentrations may vary depending on the assay used and the laboratory reference range.
[b] Weight is in terms of actual body weight. Limited information is available regarding dosing of patients significantly above ideal body weight; consider using an adjusted body weight for these patients.
[c] Up to a maximum of phosphorus 45 mmol (potassium 66 mEq) as a single dose.
Abbreviations: mEq = milliequivalents; mmol = millimoles

The adult dosage of phosphorus in PN is based upon Sodium Phosphates Injection, USP and adapted to a total daily dosage, consistent with ASPEN, rather than a dosage per liter or per amount of dextrose (calories). The daily dosages in the label (shown in Table 16) are general recommendations. The dosage should be individualized based upon the patients' clinical

condition, nutritional requirements, and the contribution of oral or enteral phosphorus and potassium intake. The amount of phosphorus that can be added to PN may also be limited by the amount of calcium that is also added to the solution.

Table 16. Recommended Daily Dosage of Potassium Phosphates Injection for Parenteral Nutrition for Adults and 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 and Older	*20 mmol/day to 40 mmol/day[a] (potassium 29.3 mEq/day to 58.7 mEq/day)*

[a] In patients with moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2), start at the low end of the dosage range.
Abbreviations: mEq = milliequivalents; mmol = millimoles

Because both phosphorus and potassium are primarily renally eliminated, patients with moderate renal impairment to (eGFR >30 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2) receiving the product for either indication should start at the low end of the dosage range. The product is contraindicated in patients with eGFR <30 mL/min/1.73 m^2 or ESRD.

Infusion Rate in Intravenous Fluids

The rate of administration should take into consideration the patient and the specific institution policy. Infusion recommendations are provided based upon age of the patient, type of access (peripheral versus central venous catheter), and need for continuous ECG monitoring. These recommendations are related to the amount of phosphorus and potassium in the product and are based on general clinical knowledge and practice guidelines and are also consistent with clinical trials of intravenous phosphate administration in adults with severe hypophosphatemia.

Concentration and intravenous infusion rate

- *The concentration of the diluted solution [see Table 1 [Table 15], Dosage and Administration (2.1)] and the infusion rate is dependent upon whether administration will be through a peripheral or central venous catheter. The maximum recommended infusion rates are shown in Table 3 [Table 17] for adults and pediatric patients 12 years of age and older.*

Table 17. Maximum Recommended Infusion Rate of Potassium Phosphates Injection for Adults and Pediatric Patients 12 Years of Age and Older

Route of Administration	***Maximum Infusion Rate***
Peripheral venous catheter	*Phosphorus 6.8 mmol/hour (potassium 10 mEq/hour)*
Central venous catheter	*phosphorus 15 mmol/hour (potassium 22 mEq/hour)*

Abbreviations: mEq = milliequivalents; mmol = millimoles

Continuous ECG monitoring and infusion through a central venous catheter is recommended for infusion rates higher than:

- *Potassium 10 mEq/hour for adults and pediatric patients weighing 20 kg or greater*
- *Potassium 0.5 mEq/kg/hour for pediatric patients weighing less than 20 kg*

Monitoring

For both indications, serum concentrations of phosphorus, potassium, calcium, and magnesium should be monitored to adjust dosage and to minimize ARs.

4. CONTRAINDICATIONS

The product is contraindicated in patients with various laboratory abnormalities (hyperkalemia; hyperphosphatemia; hypercalcemia or significant hypocalcemia) and in patients with severe renal impairment or ESRD.

5. WARNINGS AND PRECAUTIONS

The following risks are discussed:

5.1. Serious Cardiac Adverse Reactions With Undiluted, Bolus, or Rapid Intravenous Administration

This section was based on postmarketing FAERS cases of inappropriate administration (see Section 8.2.4.3 of this review).

5.2. Pulmonary Embolism Due to Pulmonary Vascular Precipitates

This section is "class labeling" for PN products and is based on postmarketing and literature cases identified in the review of other related products.

5.3. Hyperkalemia

This section describes the ARs associated with the potassium component of the product and patients at risk (severe renal impairment and ESRD, cardiac disease, or severe adrenal insufficiency, and those treated concurrently with other drugs that are known to increase serum potassium concentrations).

5.4. Hyperphosphatemia and Hypocalcemia

Hyperphosphatemia was reported in the clinical literature with high doses of intravenous potassium phosphates. The relationship between hyperphosphatemia causing subsequent hypocalcemia and related complications is described, along with recommendations to monitor serum phosphorus and calcium concentrations during and following administration.

5.5. Aluminum Toxicity

Wording from the CFR 201.323e was adapted as described below:

- "This product" was replaced with the drug product (Potassium Phosphates Injection)
- "kidney function is impaired" was replaced with "renal impairment" to be consistent with other sections of labeling.

- "Premature neonates" was replaced by "preterm infants" because the affected patient population may extend beyond the first 28 days of life, as defined in guidance for industry *E11 (RI) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population* (FDA 2018).

- Risk mitigation was added (final two paragraphs) to describe and limit total daily exposure to aluminum in the final prepared PN solution.

  Potassium Phosphates Injection contains aluminum that may be toxic.

  Aluminum may reach toxic levels with prolonged parenteral administration in patients with renal impairment. Preterm infants are particularly at risk for aluminum toxicity because their kidneys are immature, and they require large amounts of calcium and phosphate containing solutions, which also contain aluminum.

  Patients with renal impairment, including preterm infants, who receive greater than 4 to 5 mcg/kg/day of parenteral aluminum can accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

  Exposure to aluminum from Potassium Phosphates Injection is not more than 1.4 mcg/kg/day when patients are administered the recommended dosage [see Dosage and Administration (2.4), Description (11)].

  When prescribing Potassium Phosphates Injection for use in parenteral nutrition solutions containing other small volume parenteral products, the total daily patient exposure to aluminum from the admixture should be considered and maintained at no more than 5 mcg/kg/day [see Use in Specific Populations (8.4)].

Based on literature cases, see Section 8.2.4.7 of the review.

5.7. Vein Damage and Thrombosis

Class labeling for PN products discussing administration by a peripheral versus central catheter; the choice of which is dependent upon the osmolarity of the final solution. The warning also applies to thrombophlebitis with peripherally administration of hypertonic solutions, including concentrated potassium phosphates solution.

5.8. Laboratory Monitoring

Provides general recommendations for monitoring of serum phosphorus, potassium, calcium and magnesium serum concentrations during treatment.

6. ADVERSE REACTIONS

Adverse reactions as described in the Warnings and Precautions section of the label and as reported in postmarketing are included. See Section 8.2.4 of this review.

7. DRUG INTERACTIONS

The risk of hyperkalemia when the product is co-administered with other drugs that increase serum potassium concentrations is described. Several examples of drugs that are known to commonly raise potassium concentrations are included.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy and 8.2 Lactation

See Section 8.2.8 of this review.

8.4 Pediatric Use

The indicated populations and the risks associated with aluminum toxicity are described. See Section 10 in this review.

8.5 Geriatric Use and 8.6 Renal Impairment

Potential risks associated with renal excretion of phosphorus and potassium are described along with recommendations for geriatric patients with decreased renal function and patients with varying degrees of renal impairment.

10. OVERDOSAGE

Risks of hyperphosphatemia, hyperkalemia, and general recommendations for management are included. Risks are based on FAERS reports for hyperphosphatemia (see Section 8.2.4 in this review), and general medical knowledge for hyperphosphatemia and hyperkalemia.

12. CLINICAL PHARMACOLOGY

12.3. Pharmacokinetics

Limited information is provided on the distribution and elimination of phosphorus (see Section 6.3.1 of this review).

13. NONCLINICAL TOXICOLOGY

This section was removed as there is no information to convey.

14. CLINICAL TRIALS

This section was not included.

12. Risk Evaluation and Mitigation Strategies

The benefit-risk profile for Potassium Phosphates Injection, USP is favorable, and any potential risks can be mitigated through product labeling (see Section 11). Risk mitigation strategies are included in the prescribing information to reduce the incidence of dilution and administration errors that have been observed with use of similar products. There are no additional risk management strategies required beyond the recommended labeling.

13. Postmarketing Requirements and Commitments

One postmarketing commitment related to product quality will be issued for the assay results from the previously conducted TPN admixture study (described in Section 4.2.2):

3745-1 Submit the assay results of the TPN admixture studies as proposed in the TPN Admixture Compatibility Stability Protocol

Final Report Submission: 2/31/2019

Rationale for Requesting Study

The Applicant conducted a compatibility study to demonstrate the safety and efficacy of admixing the drug product with PN. The Applicant provided the results for visible and subvisible particulate matters testing during the review cycle, which addressed the safety concern of any potential precipitation (especially of calcium and phosphate). Although no precipitation was visually observed during the admixing studies, the Applicant was not able to submit, prior to the PDUFA goal date, the actual assay results to confirm its strength and demonstrate that the safety and efficacy are not compromised, due to issues with the current titration method for assay and time needed for new method development. However, the Applicant has committed to submit this data by December 31, 2019, postapproval, per their communication on October 28, 2019. Since it is very unlikely that the assay results will be significantly changed given that no precipitation has been observed, it is deemed acceptable for the Applicant to submit the assay results for the TPN admixture studies postapproval.

14. Division Director Comments

The proposed indications for Potassium Phosphates Injection, USP are very similar to those of the LD, Sodium Phosphates Injection, USP (NDA 018892).

In the absence of clear dosing recommendations in the LD upon which to rely for the two indications (correction of hypophosphatemia and use in PN) for both adults and pediatric patients from birth to less than 18 years of age, the review team considered published literature that included clinical efficacy studies for both indications in adults. These were typically open-label studies that relied upon changes in serum phosphorus levels with intravenous infusion of phosphates for efficacy endpoints. This is reasonable based on the understanding of the essential role of phosphorus in many metabolic processes necessary to cellular function, and general knowledge about the normal physiological range of serum phosphorus levels. Along with the literature and the listed drug, dosing recommendations also considered clinical guidelines, oral dietary requirements, postmarketing information and clinical experience.

14.1. Dosing for Indication of Correction of Hypophosphatemia

For this indication, the Dosage and Administration section of the LD labeling states that "the dose and rate of administration are dependent upon the individual needs of the patient" and "serum sodium, phosphorus, and calcium levels should be monitored as a guide to dosage," but no specific dosage is mentioned for any age groups. The Applicant proposed weight-based dosing for all ages that accounts for three levels of severity of baseline hypophosphatemia using serum phosphorus levels. The dosing recommendations for adults for this indication for Potassium Phosphates Injection, USP are based upon the reviewed literature, and specify weight-based dosing that accounts for three levels of severity of baseline hypophosphatemia using serum phosphorus levels. For pediatric patients, the same dosing algorithm is proposed, based on similarity of phosphorus requirements, and the equivalent physiology of IV phosphorus repletion in adults and pediatric patients; however, it is noted that the lower end of the reference range (used to define hypophosphatemia and thereby the need for correction) for infants less than 12 months of age is higher than that in adult and older pediatric patients. Based upon clinical requirements, some patients may require a higher or lower dose.

The maximum recommended initial or single dose for correction of hypophosphatemia is phosphorus 45 mmol, due to the risk of serious cardiac ARs reported with undiluted, bolus, or rapid IV administration (i.e., 50 mmol and above and/or administered over 1 to 3 hours). No daily maximum dose is specified for this indication. It is recognized that patients may require more than a single dose. Subsequent doses will be determined based upon serum phosphorus and potassium levels. Labeling will clearly discuss concentrations that warrant infusion through a peripheral line versus central venous access, and appropriate rates of administration, which also depend on the potassium component of the product, along with recommended ECG monitoring for higher infusion rates. These recommendations are based on published literature

and established practice guidelines, and will address safety issues identified in the review of FAERS postmarketing safety reports.

14.2. Dosing for PN Indication

In patients on PN, the LD recommends a phosphorus dosage of approximately 12 to 15 mmol/day per liter of PN fluid containing 250 g dextrose. The LD's dosage recommendation for use in PN does not distinguish between adults and pediatric patients 12 years and older; the only age subgroup with a distinct dosing recommendation is infants, who have a recommended dosage of 1.5 to 2 mmol/kg/day.

For Potassium Phosphates Injection, USP, the dosing recommendation for adults and pediatric patients 12 years and older is 20 to 40 mmol/day added to PN, based on published literature in adults. The dosage should be individualized based upon the patients' clinical condition, nutritional requirements, and the contribution of oral or enteral phosphorus and potassium intake. The Division's recommended simplified dosage regimen of a fixed dose range generally equates to the LD dosage. The recommended dose range in pediatric patients 12 years and older is the same as that for adults, based on the knowledge that phosphorus requirements are similar for both populations. Recommended dosages for infants and pediatric patients under 12 years of age are weight-based, and reflect the higher phosphorus needs in infants compared to older pediatric and adult patients.

Per the recommended dosing, patients in the indicated populations will not be exposed to more than the CFR-specified 5 mcg/kg/day of aluminum.

14.3. Other Safety Considerations

An additional difference between the proposed product and the LD is the salt – the LD contains sodium, while the current product contains potassium, administration of which poses a risk of hyperkalemia and associated serious cardiac AEs at higher doses and/or rapid infusion rates. Safety of the potassium component of the current product was assessed based on published literature and experience from long-standing clinical use of unapproved potassium phosphates injection products in adults and pediatric patients; the Applicant also relied upon findings of safety for the LD Potassium Chloride Injection (NDA 020161). Labeling will indicate that the product is not for use in patients with baseline potassium >4 mEq/dL due to concern for hyperkalemia, and that an alternate source of phosphorus should be used in such patients. The need to dilute Potassium Phosphates Injection, USP prior to administration and maximum infusion rates for peripheral and central venous administration will be prominently labeled.

14.4. Postmarketing Requirement/Postmarketing Commitment

The Applicant conducted compatibility/stability studies of the product in crystalloid fluids (NS and D5W) and in PN. Full results of the crystalloid compatibility study were provided, and the Applicant provided results from the PN admixture and compatibility study on visual description, pH, and particulate matters. Assay results from this study were not able to be reported prior to

the goal date due to method development. Because no precipitation was noted in this study, the CMC team deemed it very unlikely that the assay results will raise any concern regarding possible decreases in the levels of phosphorus or potassium after admixture with other PN components. For this reason, I concur that these results may be submitted as a CMC postmarketing commitment, and that the lack of these assay results do not constituent a bar to approval.

14.5. Conclusion

In recommending approval of this NDA for Potassium Phosphates Injection, the review team relied upon the previous findings of safety and effectiveness of the LD (NDA 018892) for adults and pediatric patients with respect to the active moiety of phosphorus. While complete dosing recommendations were absent in the LD, there was no suggestion that differential dosing was needed for adults and pediatric patients for correction of hypophosphatemia or for adults and pediatric patients 12 years of age and older for use in PN. Dosing for use in PN provides for weight-based dosing in pediatric patients from birth to less than 12 years, and accounts for the higher nutritional need for phosphorus for infants less than 12 months. The review team relied upon the published adult literature, as well as clinical guidelines, oral dietary requirements, postmarketing information and clinical experience. I concur with the recommendation from the review team that this product be approved.

15. Appendices

15.1. References

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15.2. Financial Disclosure

No clinical studies were conducted.

15.3. Division of Medication Error Prevention and Analysis Review

Our evaluation of the proposed Potassium Phosphates Injection, USP PI, container labels, and carton labeling identified areas of vulnerability that may lead to medication errors. PI recommendations were communicated to the Applicant during the review and incorporated into Section 11 above.

On September 20, 2019, DMEPA confirmed that previous recommendations regarding potassium phosphates (NDA 212121) were implemented in this NDA.[1]

Containers and carton labeling recommendations were communicated to the Applicant on October 24, 2019 , November 8, 2019, and November 14, 2019. The revised carton and container labels received on November 18, 2019 are acceptable from medication error perspective. See DMEPA reviews dated October 15, 2019, November 14, 2019, and November 20, 2019.

15.4. Neonatal-Perinatal Consultation

The Office of Pediatric Therapeutics was consulted to address the concentration and maximum rate of infusion of the proposed product in neonatal patients. See review by Suna Seo, October 31, 2019. The following information was extracted from that review:

A typical neonate would have an average daily maintenance total fluid requirement of ~150 mL/kg/day (ranging from 100 mL/kg/day for infants >1500 g to 200 mL/kg/day for infants <750 g); therefore, the Applicant's proposed preparation instruction for the Kphos bolus volumes using 100 mL or 250 mL would result in fluid overload.

Considering a hypothetical preterm infant with a birthweight of 1 kg, the total daily fluid requirement for the infant would be 150 to 200 mL/day. Furthermore, given that neonatal resuscitation bolus volumes typically range between 10 to 20 mL/kg/dose, any small volume intravenous bolus administration should be no more than 10 mL/kg/dose; and ideally, the dilution solution volume for dose preparation of Kphos should be far less than 5 to 10 mL.

Since a typical neonate could receive 15 to 20 IV medications daily, in general, drugs administered intravenously should not be required to be administered in a fixed volume (Sherwin et al. 2014; Ypeda 2014; Allegaert et al. 2018; O'Brien et al. 2019). It is preferable to investigate and report the minimum and maximum concentration at which the drug is sufficiently stable and to note any restrictions that this may pose for vascular access or co-administrations in a typical clinical setting (Sherwin et al. 2014; Ypeda 2014).

[1] See 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.

NeoFax recommends the maximum concentrations (for central line administration in neonates of 40 mEq/L (4 mEq/100mL) for peripheral and 80 mEq/L (8 mEq/100mL) for central venous infusions); it appears that the maximum concentration recommendation has been adhered to in most practice guidelines.

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Supervisory Pharmacologist	Sushanta Chakder	OND/ODEIII/DGIEP	**Sections: 5** **Reviewed/Edited: 5** **Appendices:**	**Select up to two:** ___Authored _X_Cleared
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Clinical Pharmacology Team Leader	Insook Kim	OTS/OCP/DCPIII	**Sections: 6** **Reviewed/Edited/Cleared:** **6**	**Select up to two:** ___Authored _X_Cleared
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Associate Director Signatory	Lisa Soule	CDER/OND/ODEIII	Section Authored: 14 Cleared: All	**Select up to two:** __X_Authored _X_Cleared
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Clinical Team Leader and Associate Director for Labeling	Joette Meyer	OND/ODEIII/DGIEP	Section Authored: ALL Reviewed/Edited/Cleared: ALL	**Select up to two:** X_Authored X__Cleared
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Clinical Reviewer	Ruby Mehta	OND/ODEIII/DGIEP	Sections Authored: 1, 2, 3, 7, 8,9, 12, 13, 15 Reviewed/Edited/Cleared: ALL	**Select up to two:** _X_Authored _X_Cleared
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DPV Team Leader	Paolo Fanti		Sections Authored: Reviewed/Edited/Cleared: 8.2.5 Safety Concerns Identified Through Post-Market Experience	**Select up to two:** ___Authored _X_Cleared
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DPV Deputy Director	Monica Munoz		Sections Authored: Reviewed/Edited/Cleared: 8.2.5 Safety Concerns Identified Through Post-Market Experience	**Select up to two:** ___Authored _X_Cleared
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