NDA/BLA Multi-Disciplinary Review and Evaluation

Application type	NDA
Application number(s)	212121
Priority or standard	Priority
Submit date(s)	3/18/2019
Received date(s)	3/19/2019
PDUFA goal date	9/19/2019
Division/office	Division of Gastroenterology and Inborn Errors Products (DGIEP)/Office of Drug Evaluation III (ODE III)
Review completion date	9/19/2019
Established/proper name	POTASSIUM PHOSPHATES INJECTION
(Proposed) trade name	None
Pharmacologic class	Parenteral Phosphorus Replacement
Code name	
Applicant	CMP Development LLC
Dosage form	Injection: phosphorus 45 mmol/15 mL (3 mmol/mL) and potassium 71 mEq/15 mL (4.7 mEq/mL) in a single-dose vial.
Applicant-proposed dosing regimen ***(continued below)***	The dose and rate of infusion of the proposed product are dependent on the individual needs of the patient: <u>For treatment of hypophosphatemia:</u> *Adults*: The maximum dosage is 45 mmol phosphorus per day. Dosage may be determined based per kg body weight or a fixed dose regimen. The following recommended dosages are suitable for most patients: phosphorus 0.16 mmol/kg to 0.64 mmol/kg (or (b) (4) However, based on clinical requirements, some patients may require higher or lower dosages. (b) (4)

Applicant-proposed dosing regimen *(continued)*	(b) (4) [redacted]
Applicant-proposed indication(s)/population(s)	In adults and adolescent patients 12 to <18 years of age: • 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. • an additive for preparing specific parenteral fluid formulas when the needs of the patient cannot be met by standard electrolyte or nutrient solutions.
Applicant-proposed SNOMED CT indication disease term for each proposed indication	
Recommendation on regulatory action	Approval for both phosphorus replacement in intravenous fluids and in total parenteral nutrition
Recommended indication(s)/population(s) (if applicable)	POTASSIUM PHOSPHATES INJECTION is a phosphorus replacement product indicated as a source of phosphorus: • in adults and pediatric patients 12 years of age and older: in intravenous fluids to correct hypophosphatemia when oral or enteral replacement is not possible, insufficient or contraindicated. • in adults weighing at least 45 kg and pediatric patients 12 years of age and older weighing at least 40 kg: for parenteral nutrition when oral or enteral nutrition is not possible, insufficient or contraindicated.
Recommended SNOMED CT indication disease term for each indication (if applicable)	
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
DRISK=Division of Risk Management
EA Environmental Analysis
DPMH=

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ESRD	end stage renal disease
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
ICU	intensive care unit in a hospital
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
L	liter
MedDRA	Medical Dictionary for Regulatory Activities

MDD	maximum daily dose
mITT	modified intent to treat
mEq	milliequivalents
mmol	millimoles
NaCl	sodium chloride
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NF	National Formulary
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PeRC	Pediatric Research Committee
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PN	parenteral nutrition
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
PN	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 45 mmol/15 mL (3 mmol/mL) and potassium 71 mEq/15 mL (4.7 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 supplied as a 15 mL partial fill single-dose glass vial and is administered, after dilution or admixing, by intravenous route for phosphorus replacement.

The Applicant, CMP Development, LLC (CMP), is not proposing a proprietary name. The Established Pharmacologic Class will be "parenteral phosphorus replacement." The non-proprietary name is POTASSIUM PHOSPHATES INJECTION, USP.

Each mL contains 175 mg of monobasic potassium phosphate, NF, monohydrate and 300 mg of dibasic potassium phosphate, USP.

The Applicant-proposed indications were:

- 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.
- As an additive for preparing specific parenteral fluid formulas (e.g., total parenteral nutrition [PN]) when the needs of the patient cannot be met by standard electrolyte or nutrient solutions.

The indications recommended for approval are:

> **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 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 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.

The Applicant submitted a 505(b)(2) application based on published literature and a listed drug (LD) Sodium Phosphates Injection, 45 mmol phosphorus (3 mmol /mL) distributed by Hospira, Inc. (NDA 018892). 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." Sodium monobasic phosphate, sodium dibasic phosphate, and potassium monobasic phosphate and potassium dibasic phosphate are different active ingredients; they are all salts. However, they all have the same active moiety, phosphate. Both products provide repletion of phosphorus for correction of hypophosphatemia by the same mechanism of action.

No single-ingredient oral sodium phosphates products or any potassium phosphates products are FDA-approved. However, there are 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. Both sodium and potassium phosphates injection products are frequently on national drug shortage.

The concentration of phosphate in the proposed to-be-marketed POTASSIUM PHOSPHATES INJECTION, USP product is the same as in two of the marketed unapproved potassium phosphates injection products, but the concentration of potassium in the proposed product is slightly higher at (4.7 mEq/mL) compared to the marketed unapproved products (4.4 mEq/mL).

Dosing of POTASSIUM PHOSPHATES INJECTION, USP is dependent on the indication, see Section 11 – Labeling, for a complete discussion of dosing.

1.2. Conclusions on the Substantial Evidence of Effectiveness

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

NDA 212121 relies on the FDA's previous findings of safety and effectiveness for the LD, SODIUM PHOSPHATES INJECTION, USP by Hospira, which is indicated for all age groups. However, dosing recommendations for the LD are not provided for the indication of correction of hypophosphatemia in any age group. Dosing for use in PN is provided for adults and infants but not for any other pediatric age group. For both indications, there is nothing in the LD labeling that indicates that differential dosing is needed for adults and for pediatric patients 12 years of age and older.

Therefore, to support dosing regimens for both indications, NDA 212121 also relies on published clinical efficacy studies in adults and the long-standing clinical experience and guidelines based on the published literature (See Table 5 and Table 7).

There are no controlled clinical studies of potassium phosphates in pediatric patients in the published literature. Dosing for pediatric patients 12 years and older is derived from adult data that identified a dosing algorithm that resulted in correction of hypophosphatemia, given the similar phosphorus requirements and understanding of the physiology of phosphorus repletion over both adults and pediatric patients 12 years and older. The recommended dose range for use in PN 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.

Additionally, the safety of the potassium salt is supported by the published literature of other intravenous potassium-containing products (see Table 9) and the clinical guidelines based on this published literature.

The Applicant is requesting approval for adults and limited to pediatric patients age 12 and older for both indications. In addition to the age limit, the Applicant also proposed a maximum daily dose of phosphorus (b) (4) in pediatric patients 12 years of age and older for the correction of hypophosphatemia indication. The Applicant did not propose a maximum daily dose for the PN indication. The review team did not agree with the Applicant's rationale for these choices (see discussion below).

The proposed pediatric age and dose limit for use in PN is due to the aluminum content of the product (See Section 8.1). The Applicant is currently requesting a deferral of the pediatric assessment in patients less than 12 years of age until an age-appropriate formulation is developed. To have a consistent pediatric population definition for both indications, and to minimize the risk of dosing errors, the indication is also limited to adults and pediatric patients 12 years of age and older for the correction of hypophosphatemia indication.

Dosing recommendations for SODIUM PHOSPHATES INJECTION, USP in PN are provided in the LD's labeling for adults (characterized per Liter of PN containing 250 g of Dextrose) and infants (characterized per kg), but not for other pediatric age groups. The labeled dosing in PN for the current product is based on the literature submitted, and is limited to a maximum daily dose of 40 mmol phosphorus in pediatric patients 12 years of age and older weighing at least 40 kg and to a maximum daily dose of 45 mmol phosphorus in adults weighing at least 45 kg. These restrictions are due to the aluminum content of the product (See Section 8.1).

For the correction of hypophosphatemia indication, the review team agrees with the indicated population but does not agree that a maximum daily dosage limit is needed for either adults or pediatric patients 12 years of age and older due to the anticipated short-term use of the product. The review team agrees with the Applicant's proposed dosing range (phosphorus 0.16 mmol/kg to 0.64 mmol/kg), but has proposed 3 specific doses based on baseline serum phosphorus concentrations (0.16 to 0.31 mmol/kg, 0.32 to 0.43 mmol/kg and 0.44 to 0.64 mmol/kg). The maximum initial or single dose of phosphorus is 45 mmol based upon safety concerns, including serious and life-threatening cardiac adverse reactions, with administration of higher single doses or rapid infusion (see Section 8.1.5).

For the use in PN, the aluminum content of the product raises concerns due to the potentially chronic use of the product, and the FDA regulations regarding maximum daily exposure to aluminum (21 CFR 201.323). Therefore, the review team has proposed limiting the maximum dosage of phosphorus for the PN indication in adults weighing at least 45 kg to 45 mmol/day, and in pediatric patients 12 years of age and older weighing at least 40 kg to 40 mmol/day. The (b) (4) The review team has proposed a generally recommended phosphorus dosage independent of the volume and (caloric) content of the PN solution (i.e., 20 to 40 mmol/day), based on the average caloric need of an adolescent or adult (See Section 8.1.6).

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 post-marketing commitment (PMC) (see Section 13). The Applicant commits to submit these assay studies by October 31st, 2019. All inspections have been performed and the drug substance and drug product are acceptable to the Chemistry, Manufacturing and Controls reviewers. A PREA post-marketing requirement (PMR) will be issued to develop a lower aluminum content formulation, and the Applicant has agreed to a timeline for completion of December 2020. This application is recommended for approval.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

NDA 212121 Risk/Benefit Summary

Phosphorus is one of the most abundant elements in the human body. Phosphorus is primarily an intracellular anion and thus, an estimation of total body phosphorus levels in not clinically feasible. Phosphorus has a variety of biochemical functions in the body including many metabolic and enzyme reactions in almost all organs and tissues. Specifically, it exerts a modifying influence on the steady state of calcium levels, a buffering effect on acid-base equilibrium, a primary role in the renal excretion of hydrogen ions and plays an essential role in oxygen transport. Hypophosphatemia is common in hospitalized patients and especially prevalent in severely ill patients, with reports as high as 30-40%. Clinical features of hypophosphatemia include muscle weakness, rhabdomyolysis, hemolysis, respiratory failure and heart failure, seizures and coma. Infusion of phosphate products can be life-saving if administered correctly; however, if inappropriately administered, can cause significant morbidity or death.

Hypophosphatemia is generally corrected with oral replacement if mild or moderate in severity, unless the patient is unable to tolerate oral feedings or medications. However, severe hypophosphatemia (serum phosphorus levels < 1mg/dL), which can be life-threatening, should be corrected intravenously. SODIUM PHOSPHATES INJECTION, USP (the LD) is the only FDA-approved drug indicated in adults and pediatric patients as a source of phosphorus to prevent or correct hypophosphatemia or as an additive to parenteral nutrition (PN). There are two unapproved injectable potassium phosphates products on the market, which have been in clinical use for many years. Marketed unapproved potassium phosphates products and the approved SODIUM PHOSPHATES INJECTION, USP are frequently on the national drug shortage list. The choice to use sodium or potassium salt for phosphorus repletion primarily depends on a patient's baseline sodium and potassium levels. Based on extensive clinical experience, potassium phosphates should be avoided when the patient's serum potassium is greater than 4 mEq/L to minimize the potential for hyperkalemia. Replacement of the unapproved marketed formulations with an approved product will ensure product quality and availability.

There were no clinical studies performed for this approval by the Applicant. NDA 212121 relies on the FDA's previous findings of safety and effectiveness for the Listed Drug (LD), SODIUM PHOSPHATES INJECTION, USP, which is indicated for all age groups for as a source of phosphorus for correction of hypophosphatemia and in PN. However, dosing recommendations for the LD are not provided for the indication of correction of hypophosphatemia in any age group. Dosing for use in PN is provided for adults and

infants but not for any other pediatric age group.

Therefore, to support dosing regimens for both indications, NDA 212121 also relies on published clinical efficacy studies in adults and the long-standing clinical experience and guidelines based on the published literature.

There are no controlled clinical studies of potassium phosphates in pediatric patients in the published literature. Dosing for pediatric patients 12 years and older is derived from adult data that identified a dosing algorithm that resulted in correction of hypophosphatemia, given the similar phosphorus requirements and understanding of the physiology of phosphorus repletion over both adults and pediatric patients 12 years and older. The recommended dose range for use in PN 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.

Additionally, the safety of the potassium salt is supported by the published literature on other intravenous potassium-containing products and the clinical guidelines based on this published literature.

There are significant risks associated with injectable potassium phosphates, which require that it be diluted appropriately and that the correct rate be administered, to avoid exceeding the maximum for peripheral and central line infusion as noted in the labeling. Higher rates of infusion have been associated with adverse events including hyperphosphatemia, hypocalcemia, hyperkalemia and calcium-phosphate precipitates resulting in pulmonary embolism or renal injury. Rapid administration of potassium is known to cause cardiac arrhythmias, QT interval prolongation, cardiac arrest and death; these risks should be considered for any intravenous potassium-containing products. Use of potassium phosphates is contraindicated in patients with hypercalcemia or significant hypocalcemia, hyperphosphatemia, hyperkalemia, severe renal impairment (eGFR less than 30 mL/min/1.73m^2) and end stage renal disease (ESRD).

The dose of potassium phosphates to correct hypophosphatemia must be individualized to the patient's clinical condition, underlying disease, renal function, baseline serum phosphorus, potassium and calcium levels. The dosage recommendations are provided in millimoles per kilogram (based on clinical experience that this is the most reliable method for phosphorus dosing) and the dose is selected based on the baseline serum phosphorus level (see Table 3). The maximum dose per administration should not exceed 45 mmol (0.64 mmol/kg is approximately 45 mmol in a 70 kg adult). There is no maximum daily dose recommended. Additional doses should be based on serum phosphorus, potassium and calcium levels in addition to clinical evaluation. Hypomagnesemia is common in patients with hypophosphatemia and should also be routinely monitored for and appropriately corrected.

Potassium phosphates are also used as a source of phosphorus in PN. Proper preparation and administration are important to prevent calcium-phosphate precipitates in the solution and after infusion in the patient. Doses of 20 to 45 mmol daily (14 to 17 mmol per 1000 calories) nutrition are generally required to maintain normal phosphorus levels; however, the dose should continue to be adjusted based on the patients' clinical condition and serum phosphorus levels.

CMP Development LLC's product contains aluminum at a specification that could exceed that allowed daily exposure for pediatric patients under age 12 and for lower weight adults, and therefore the indication for PN will be restricted such that adults weighing 45 kg or greater receive a maximum of phosphorus 45 mmol/day, and children 12 of age and older weighing at least 40 kg receive a maximum of phosphorus 40 mmol/day, until a lower aluminum formulation of POTASSIUM PHOSPHATES INJECTION, USP is developed. To have a consistent pediatric population definition for both indications, and to minimize the risk of dosing errors, the target population for the correction of hypophosphatemia indication is also limited to adults and pediatric patients 12 years of age and older.

The overall benefit/risk assessment for POTASSIUM PHOSPHATES INJECTION, USP is favorable for approval. The benefit of the drug outweighs the risks, which can be mitigated with proper dose and administration as per the labeling.

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 not clinically feasible. 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 the body and is involved in many metabolic and enzyme reactions in almost all organs and tissues. It exerts a modifying influence on the steady state of calcium levels, a buffering effect on acid-base equilibrium, and a primary role in the renal excretion of hydrogen ions.	Phosphorus levels should be monitored in hospitalized or severely ill patients. The dose and rate of administration of phosphates are dependent upon the individual needs of the patient. See Section 11 – Labeling. Infusion of potassium phosphate products can be life-saving or life-threatening and benefit depends on appropriate administration, using the correct dose(s), dilution, rate of administration, and monitoring, all of which are necessary for safe and effective use.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Phosphorus is involved in aerobic and anaerobic energy metabolism. It 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 (DPG), which plays a crucial role in O_2 delivery to tissues. Hypophosphatemia is common in hospitalized and especially prevalent in severely ill patients. See Section 2.1 analysis of condition. Clinical features of hypophosphatemia include muscle weakness, rhabdomyolysis, hemolysis, respiratory failure and heart failure, seizures and coma.	
Current Treatment Options	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. SODIUM PHOSPHATES INJECTION, USP (the LD) is an approved product indicated "as a source of phosphorus, for addition to large volume intravenous fluids to prevent or correct of hypophosphatemia in patients with restricted or no oral intake and as an additive for preparing specific parenteral fluid formulas when the needs of the patient cannot be met by standard electrolyte or nutrient solutions." However, it is not always appropriate to use sodium phosphates, due to associated risks of excessive amounts of sodium, which can result in complications of fluid overload. The decision to use the sodium or potassium phosphates salt depends on the individual patient's electrolyte status. There are two marketed unapproved injectable potassium phosphate products that have been in clinical use for many years and are frequently on the national drug shortage list. SODIUM PHOSPHATES INJECTION, USP is also frequently on the national drug shortage list.	Replacement of unapproved marketed product(s) with an approved formulation of injectable potassium phosphates would provide assurance of product quality and availability. Sodium phosphates is not always the appropriate choice for phosphorus replacement from a safety perspective. Both potassium and sodium phosphates injection products are critical to public supply and patient needs.
Benefit	Unapproved marketed products may be variable in quality standards. POTASSIUM PHOSPHATES INJECTION, USP demonstrated acceptable quality and manufacturing controls.	The totality of the evidence supports efficacy of: **In Intravenous Fluids to Correct Hypophosphatemia**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Literature review supports the importance of correcting hypophosphatemia, which can result in serious adverse events or death NDA 212121 relies on the FDA's previous findings of safety and effectiveness for the LD, SODIUM PHOSPHATES INJECTION, USP, which is indicated for all age groups for the indications of correction of hypophosphatemia and use of phosphorus in parenteral nutrition (PN). NDA 212121 relies on the FDA's previous findings of safety and effectiveness for the LD, SODIUM PHOSPHATES INJECTION, USP by Hospira, which is indicated for all age groups. However, dosing recommendations for the LD are not provided for the indication of correction of hypophosphatemia in any age group. Dosing for use in PN is provided for adults and infants but not for any other pediatric age group. For both indications, there is nothing in the LD labeling that indicates that differential dosing is needed for adults and for pediatric patients 12 years of age and older. Therefore, to support dosing regimens for both indications, NDA 212121 also relies on published clinical efficacy studies in adults and the long-standing clinical experience and guidelines based on the published literature. There are no controlled clinical studies of potassium phosphates in pediatric patients in the published literature. Dosing for pediatric patients 12 years and older is derived from adult data that identified a dosing algorithm that resulted in correction of hypophosphatemia, given the similar phosphorus requirements and understanding of the physiology of phosphorus repletion over both adults and pediatric patients 12 years and older. The recommended dose range for use in PN 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.	POTASSIUM PHOSPHATES INJECTION, USP 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 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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	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 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. Assay results for the PN admixture study are pending at the time of approval, but are not considered necessary for the safety assessment.	
Risk and Risk Management	• Cardiac adverse reactions including death from inappropriate administration (i.e., undiluted bolus, or rapid intravenous administration). • Electrolyte abnormalities including: ○ Hyperkalemia, with associated complications including nausea, vomiting, paresthesias, muscle weakness and paralysis can result from administration of potassium phosphates, especially in patients with adrenal insufficiency and renal insufficiency or baseline hyperkalemia. • Calcium precipitation: Too rapid or high dose administration may result in renal failure secondary to precipitation in the renal tubules or precipitation systemically can cause micro-emboli to multiple organs, especially pulmonary embolism. Patients with hypercalcemia are at increased risk for calcium-phosphate precipitation. Incorrect PN preparation methods can cause precipitation in the solution. • Hyperphosphatemia can occur, especially in patients with renal impairment. • Hypocalcemia can occur, especially in association with hyperphosphatemia, leading to arrhythmias and hypocalcemic tetany.	Potential adverse reactions can be managed through prescription labeling. The product is only indicated when oral/enteral administration of phosphates is not possible, insufficient or contraindicated, or for severe hypophosphatemia. Labeling also includes recommendations for preparation and administration (dilution, central versus peripheral administration, and infusion rates), dosage recommendations, and laboratory monitoring of phosphorus, potassium, calcium and magnesium serum concentrations. See Section 11 labeling. No new safety concerns are expected in the post-market setting with this potassium phosphate product. Due to the potassium content, the product will be limited to patients with a baseline potassium of less than 4 mEq/dL for use in intravenous fluids to correct

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Hypomagnesemia is common in association with hypophosphatemia and can result from administration of phosphates injection • The proposed product contains aluminum at levels above the allowable limit of aluminum exposure to pediatric patients <12 years of age and for lower weight adults; and will not be indicated in patients <12 years of age and weighing less than 40 Kg or adult patients weighing less than 45 kg. • Phlebitis can occur with peripheral infusions.	hypophosphatemia. The maximum daily dose of potassium should not be exceeded when administering potassium phosphates, taking into account all sources of potassium. For the PN indication, the maximum dose is 40 mmol daily in pediatric patients 12 years of age and older weighing at least 40 kg, and 45 mmol for adults weighing at least 45 kg due to the aluminum content. The product will only be approved for pediatric patients 12 years of age and older for the hypophosphatemia indication also, in order to avoid possible medication errors. (See Section 10) A PREA PMR will be issued for development of an age-appropriate formulation to ensure aluminum exposure does not exceed ICH Q3D requirements. A PMC to provide the results of the assay analysis for the PN admixture studies will also be issued. Routine pharmacovigilance is recommended. There are no recommendations for risk management (REMS or FDAAA PMRs) beyond labeling recommendations.

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. It 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 (DPG) which play crucial roles in O_2 delivery to tissue. Adenosine diphosphate (ADP) 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 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 (PTH) 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 PTH 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 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. 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:

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

Serum phosphate concentration in adults normally ranges between 2.5 and 4.5 mg/dL. Net intestinal phosphate absorption from diet generally ranges between 500 and 1000 mg/day (16-32 mmol/day). Acute severe hypophosphatemia with serum phosphate <1 mg/dL (<0.32 mmol/L) 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 intensive care unit (ICU) with continuous cardiac monitoring during central venous catheter infusion of phosphorus (Bringhurst et al. 2018).

Chronic hypophosphatemia usually is 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 large amounts of phosphate-binding aluminum, usually in the form of antacids
- Ingestion of aluminum such as in some antacids, which 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. See Section 8.1.5 - Discussion of Dosing for Treatment of Hypophosphatemia and Section 11 – Labeling: Dosage and Administration.

Hypophosphatemia, especially severe hypophosphatemia, is more common in severely ill patients in the 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; Weinsier et al. 1982; Larsson et al. 1983; Thompson and Hodges 1984; Sacks et al. 1994).

Urgent treatment of hypophosphatemia is probably only required in patients with serum phosphorus levels less than 1 mg/dL.

2.1.3. Phosphorus Use in Parenteral Nutrition

See Section 8.1.2.

Parenteral nutrition (PN) 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. Total parenteral nutrition (PN) 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 reported different recommendations regarding phosphorus needs, per total energy (7–10 mmol/1000 kcal or 15–25 mmol/1000 kcal), per kilogram of body weight (0.5 mmol/kg), per daily amount (20–30 mmol/day or 9.9–14.8 mmol/day) or per volume of nutritive solution (6.2 mmol/L or 8.5–14.5 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 POTASSIUM PHOSPHATES INJECTION, USP for intravenous administration for adults in 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.

The dosage and administration information for POTASSIUM PHOSPHATES INJECTION, USP for intravenous administration to infants, children and pediatric patients in PN, is cited in several Guidelines (Kahl and Hughes 2017; Taketomo 2017), pediatric textbooks and publications. See Section 8.1.2.

Calcium and phosphorus requirements of the neonate and infant are substantially higher than those of the older child and are dramatically different from the adult requirement. The pediatric dosage and administration information in the handbooks appears to derive from adult clinical studies and established practices at various pediatric medical centers.

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. There is also one approved injectable formulation of sodium phosphates on the market (Table 1). Potassium phosphates and sodium phosphates cannot be used interchangeably, and the choice of replacement is dependent on the patients' serum electrolytes and other underlying medical conditions (e.g., renal insufficiency). Both injectable phosphates salts are frequently in shortage.

Table 1. Other Treatment Options for Hypophosphatemia or Use in PN

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 P/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.
Proposed Drug Product						
POTASSIUM PHOSPHATES INJECTION, USP	Correction of hypophosphatemia Additive to PN	N/A	3 mmol/mL of phosphorus potassium 4.7 mEq/mL	Relies on LD	See Section 8.2, Safety Review Approach	Distributed by: 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 per mL and potassium 4.4 mEq per mL The dose and rate of administration are dependent upon the individual needs of the patient	None provided in labeling	-Hypocalcemia and hyperkalemia -Hyperphosphatemia possible with overdose or pts with renal failure or adrenal insufficiency	Manufacturer - HOSPIRA, INC. 141588017)

Product s Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
POTASSIUM PHOSPHATES INJECTION, solution, concentrate, 224 of mg of monobasic and 236 mg of dibasic potassium phosphate	Treatment and prevention of hypophosphatemia Additive to PN	Unapproved	Phosphorus 3 mmol per mL, Potassium 4.4 mEq per mL The dose and rate of administration are dependent upon the individual needs of the patient	None provided in labeling	-Hypocalcemia and hyperkalemia -Hyperphosphatemia possible with overdose or pts with renal failure or adrenal insufficiency	Manufacturer - Fresenius Kabi

Note: the proposed product contains 4.7 mEq of potassium (K+ per ml, which is higher than the current marketed unapproved products at 4.4 mEq/mL.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Approved and marketed unapproved products for phosphorus repletion are represented in Table 1. Injectable forms of phosphates salts are frequently in drug shortage. The Applicant is using the approved SODIUM PHOSPHATES INJECTION, USP, (NDA 18892) as the listed drug (LD) for this 505(b)(2) Application, which also relies upon published literature.

3.2. Summary of Presubmission/Submission Regulatory Activity

IND 122149

March, 2014 – The original sponsor (codaDOSE, Inc.) requested a preIND meeting to discuss oral and injectable potassium phosphates, and written responses were communicated on April 17, 2014 and agreement was reached on a 505(b)(2) regulatory pathway.

July 19th 2016 – Sponsor changed to CMP Development LLC.

October 9th, 2017 – CMP Development LLC submitted an initial Pediatric Study Plan (iPSP) for FDA agreement.

December 13th, 2017 – PeRC Recommendations:

- The PeRC agreed with the division that there should not be a plan for a full waiver.
- The PeRC recommended that the division not agree to a deferral at the time. (b) (4) , then the PeRC would agree to support a deferral during NDA review.

December 13th, 2018 – iPSP agreement.

The agency agreed to the sponsor's iPSP. The PeRC concurred with the plan for deferral of pediatric assessment in pediatric patients less than 12 years of age and assessment of pediatrics 12 years of age and older. The sponsor agreed to develop an age-appropriate formulation with acceptable levels of aluminum content.

March 19, 2019 – NDA submitted.

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

4.1. Office of Scientific Investigations (OSI)

An OSI audit was not requested or performed given that the Applicant did not conduct any clinical trials.

4.2. Product Quality

Drug Substances

The active ingredient, monobasic potassium phosphate, is a white to off-white odorless powder. It is very soluble in water. Its melting point is >252.6°C (decompose) and crystal density is 2.33 g/cc. Its molecular formula is KH_2PO_4 and its molecular weight is 136.086.

Monobasic Potassium phosphate is manufactured by (b) (4) The complete CMC information regarding raw materials, manufacturing, purification, characterization, stability, storage and container closure is provided in DMF (b) (4) The overall quality of monobasic potassium phosphate is controlled by its specification. The particle size and polymorphs of monobasic potassium phosphate are not important because the drug product is a solution as injection. The manufacturing process, specification and stability data of monobasic potassium phosphate were deemed adequate per the drug substance reviewer.

The other active ingredient, dibasic potassium phosphate, is also manufactured by (b) (4) . The complete CMC information regarding raw materials, manufacturing, purification, characterization, stability, storage and container closure is provided in DMF (b) (4) . The overall quality of dibasic potassium phosphate is controlled by its specification. The particle size and polymorphs of dibasic potassium phosphate are not important because the drug product is a solution as injection. The manufacturing process, specification and stability data of dibasic potassium phosphate were deemed adequate per the drug substance reviewer.

The active ingredients manufactured by (b) (4) are controlled to conform to the requirements (specification) to produce POTASSIUM PHOSPHATES INJECTION, USP.

Drug Product

POTASSIUM PHOSPHATES INJECTION, USP containing phosphorus 45 mmol/15 mL (3 mmol/mL) and potassium 47 mmol/15 mL (4.7 mEq/mL), is a sterile, nonpyrogenic, concentrated solution. It contains 175 mg/mL of monobasic potassium phosphate and 300 mg/mL of dibasic potassium phosphate in Water for Injection, USP, as an additive to intravenous solutions.

The drug product is supplied as a 15 mL clear (b) (4) glass vial, closed with a (b) (4) stopper and sealed with a (b) (4) cap. There are no preservatives or anti-oxidants in this formulation, so the unused portion should be discarded.

The drug product, POTASSIUM PHOSPHATES INJECTION, USP, is manufactured by (b) (4) (b) (4) The key drug product manufacturing process includes:
(b) (4) The drug product manufacturing process was reviewed and deemed adequate for manufacturing process robustness.

The potassium phosphates injection admixture compatibility studies were conducted with 0.9% sodium chloride (normal saline), 5% dextrose in water (D5W), Clinimix-E and Kabiven. The Applicant has committed to submit the admixture assay data by October 31, 2019. As no calcium phosphate precipitates were observed in the admixtures and phosphate salts are very soluble in water, a significant change in potassium and phosphate assay results is not expected in the admixtures. Therefore, the drug product appears to be compatible with these diluents and PN solutions.

The Applicant provided adequate justification for the differences in the physiochemical properties between the proposed and the listed drug product. Consistent with 21 CFR 320.24 (b)(6), FDA deemed the information supporting the relative bioavailability of phosphorus from the proposed drug product to the listed drug to be adequate, and a biobridge has been established to the Agency's finding of safety and effectiveness for the listed drug. Thus, an additional *in vivo* bioequivalence (BE) bridging study is not needed.

The overall control strategy for the drug product's identity, strength, purity and quality was deemed adequate.

The Office of Process and Facilities (OPF) has made an "Adequate" recommendation for all facilities in this application.

A claim for a categorical exclusion from the requirements of an environmental assessment (EA) in accordance with 21 CFR Part 25.31 is granted.

A 24-month expiration dating period is granted when stored at 2°C - 8°C (36°F - 46°F) in the proposed container closure system.

The OPQ Nomenclature Committee recommended to prominently display the strength of Phosphorus and Potassium in the drug product title as shown below:

POTASSIUM PHOSPHATES INJECTION, USP
Phosphorus 45 mmol/15 mL
(3 mmol/mL)

Potassium 71 mEq/15 mL
(4.7 mEq/mL)

The labels and labeling are satisfactory from the CMC perspective.

This NDA is recommended for approval from the OPQ perspective.

Post-Marketing Commitments (PMC):

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 visual description, pH and particulate matters 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 to demonstrate that the safety and efficacy are not compromised as a result of admixture, due to delayed HPLC method development. However, the Applicant has committed to submit this data by October 30, 2019, post-approval. Since it is very unlikely that the assay results will be significantly changed when no precipitation has been observed, it is deemed acceptable for the Applicant to submit the assay results (post-approval) for the PN admixture studies (Protocol 0009 submitted in amendment 0009 dated 6/25/2019).

4.3. Clinical Microbiology

(b) (4)

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

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No nonclinical studies were conducted by the Applicant with POTASSIUM PHOSPHATES INJECTION, USP and the Applicant is relying on the Agency's previous safety assessment for the listed drug, SODIUM PHOSPHATES INJECTION, USP 45 mM distributed by Hospira (NDA 18892), to support a 505(b)(2) NDA for POTASSIUM PHOSPHATES INJECTION, USP.

The Applicant conducted an extractable and leachable assessment for the container closure system. A risk assessment of all Class 1, 2A, 2B and 3 elemental impurities recommended in the ICH Q3D was also conducted. The Applicant's specifications for elemental impurities are acceptable per ICH Q3D, and the specification limits for (b) (4) that are not addressed in ICH Q3D are considered acceptable. There are no safety concerns for the elemental impurities or leachables in the drug product from the container closure system. From the nonclinical perspective, no approvability issues have been identified for proposed product at the proposed doses.

5.2. Referenced NDAs, BLAs, DMFs

Reference Listed Drug is Sodium Phosphate, NDA 018892.

5.2.1. Other Toxicology Studies

Safety Assessment of Aluminum

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 (21 CFR 201.323).

The Applicant's aluminum specification of 15,000 mcg/L is acceptable, as the aluminum exposure does not exceed 5 mcg/kg/day for the indicated patient population of adults and pediatric patients 12 years of age and older and weighing at least 40 kg. At the maximum recommended dose of 40 mmol/day Phosphorus, patients 12 years and older (≥ 40 kg body weight) will not receive more than 4.9 mcg/kg/day of aluminum. (b) (4) For this reason, the indicated population is limited to pediatric patients 12 years of age and older (weighing at least 40 kg), and adults (weighing at least 45 kg).

Safety Assessment of Extractables/Leachables

(b) (4)

(b) (4) Overall, there appear to be no nonclinical safety concerns for the potential leachables in POTASSIUM PHOSPHATES INJECTION, USP solution based on data provided from the extractable and leachable studies.

Safety Assessment of Elemental Impurities

In the screening leachable study with the (b) (4)

Further, an evaluation of elemental levels with the potassium phosphate solution drug product, (b) (4) The Applicant's specification limits for (b) (4) are acceptable.

(b) (4)

The maximum leachable amount of (b) (4)

(b) (4)

(b) (4) ***: Maximum daily exposure is*** (b) (4) ***mg/day.***

Based on the Agency for Toxic Substances and Disease Registry for (b) (4)

(b) (4) ***: Maximum daily exposure is*** (b) (4) ***mg/day.***

According to the OECD Screening Information DataSet on (b) (4)

[1] F1 = A factor to account for extrapolation between species

[2] F2 = A factor to account for variability between individuals

[3] F3 = A variable factor to account for toxicity studies of short-term exposure

[4] F4 = A factor that may be applied in cases of severe toxicity, e.g., non-genotoxic carcinogenicity, neurotoxicity or teratogenicity. In studies of reproductive toxicity, the following factors are used

[5] F5 = A variable factor that may be applied if the no-effect level was not established

[6] F6 = A factor to account for the bioavailability of the drug

(b) (4)

(b) (4) ***Maximum daily exposure is*** (b) (4) ***mg/day.***

In children (12-17 years old) and adults (18-50 years old), the tolerable upper intake levels for (b) (4) Therefore, there are no safety concerns with the detected levels of (b) (4) from the proposed container closure system.

6. Clinical Pharmacology

6.1. Executive Summary

The Applicant proposes POTASSIUM PHOSPHATES INJECTION, USP, phosphorus 45 mmol /15 mL (3 mmol/mL) and potassium 71 mEq/15 mL (4.7 mEq/mL), for approval under the 505 (b)(2) pathway relying on the Agency's findings of safety and effectiveness for the listed drug (LD), i.e., 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. The Applicant has also provided literature data to support the effective and safe use of the proposed product. The safety of potassium in the proposed product is supported by literature only. Note that the Applicant has not conducted new clinical pharmacology studies using the proposed product to support this submission.

Of note, SODIUM PHOSPHATES INJECTION, USP (NDA 018892) is approved in pediatric patients without age restriction. (b) (4) Refer to Section 5.2.1.

In the LD labeling, the dose and rate of administration are not specified for correction of hypophosphatemia. For parenteral nutrition, the LD labeling states that approximately 12 to 15 mM 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 of phosphorus for infants receiving PN is 1.5 to 2mM P/kg/day. Therefore, published literature provided additional support for the specific dosing recommendations for the proposed potassium phosphate product.

6.1.1. Recommendations

From a Clinical Pharmacology standpoint, the NDA is acceptable to support the approval.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The clinical pharmacology information for phosphorus is primarily based on the labeling of the listed drug, 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 adenosine triphosphate (ATP) and 2,3 diphosphoglycerate (DPG), 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. The normal level of serum phosphorus is 3.0 to 4.5 mg/100 mL in adults; 4.0 to 7.0 mg/100 mL in children.

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.

6.2.2. 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 parenteral nutrition.

Compared to the LD, SODIUM PHOSPHATES INJECTION, USP, the proposed product POTASSIUM PHOSPHATES INJECTION, USP has a different salt form. Due to 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 ≥4.0 mEq/dL due to a concern of hyperkalemia.

The recommended dosages for both correction of hypophosphatemia and for parenteral nutrition are primarily based on published literature. Refer to Section 6.3.2 and Section 8.1.5 for the detailed review of published literature that supports the dosing recommendation. The dose recommendations are summarized as follows.

For Correction of Hypophosphatemia in Intravenous Fluids

The recommended phosphorus doses (as shown in the table below) 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 12 years of age and older as for adults, when considering the same daily requirement of phosphorus intake based

on similar recommended daily allowance in adults and children age 4 and older (21 CFR 201.101). Refer to Section 8.1.5.

The recommended maximum single dose is phosphorus 45 mmol (potassium 71 mEq). Greater than 50 mmol of phosphorus given as potassium phosphate injection has resulted in hyperphosphatemia, hypocalcemia, hyperkalemia and calcium/phosphate precipitation in cases reported in published literatures. In addition, there is literature that supports a maximum initial or single dose of 45-50 mmol phosphorus in adults, followed by repeat assessment of the patient. Refer to Section 8.1.2.

Table 2. Recommended Initial or Single Dose of POTASSIUM PHOSPHATES INJECTION in Intravenous Fluids to Correct Hypophosphatemia in Adults and Pediatric Patients 12 Years of Age and Older

Serum Phosphorus Concentration[a]	Phosphorus Dosage [b, c]	Corresponding Potassium Content
1.8 to 2.4 mg/dL	0.16 to 0.31 mmol/kg	0.25 to 0.49 mEq/kg
1.0 to 1.7 mg/dL	0.32 to 0.43 mmol/kg	0.5 to 0.68 mEq/kg
Less than 1 mg/dL	0.44 to 0.64 mmol/kg	0.69 to 1.0 mEq/kg

[a] Serum phosphorus reported using 2.5 mg/dL as the lower end of the reference range for healthy adults. 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 as a single dose (potassium 71 mEq

The infusion rate of the proposed product via peripheral venous catheter is up to phosphorus 6.4 mmol/hour (potassium 10 mEq/hour). For infusion rates higher than 10 mEq/hour potassium in adults and 0.5 mEq/kg/hour in pediatric patients, continuous electrocardiographic (ECG) monitoring is recommended. The recommended maximum infusion rate via a central line is phosphorus 15 mmol/hour following ECG monitoring.

For 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 and shown in the table below. Minimum body weight limits of 45 kg (adults) and 40 kg (pediatric patients), along with the maximum daily phosphorus doses of 45 mmol and 40 mmol are recommended, respectively, for these two patient populations, due to the risk of aluminum toxicity with the proposed formulation. Refer to Section 5.2.1 for comments on the aluminum content.

Table 3. Recommended Daily Dosage of POTASSIUM PHOSPHATES INJECTION for Parenteral Nutrition

Patient Population	Generally Recommended Phosphorus Daily Dosage[a, b] (Potassium Content)	Maximum Phosphorus Dosage (Potassium Content)
Adults weighing at least 45 kg	20 to 40 mmol/day potassium 31 to 62.7 mEq/day	45 mmol/day potassium 71 mEq/day
Pediatric patients 12 years of age and older weighing at least 40 kg	20 to 40 mmol/day potassium 31 to 62.7 mEq/day	40 mmol/day potassium 62.7 mEq/day

[a] Individualize the dosage based upon the patient's clinical condition, nutritional requirements, and the contribution of oral or enteral phosphorus and potassium intake. The amount of phosphorus that can be added to parenteral nutrition may be limited by the amount of calcium that is also added to the solution.
[b] 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.

See Section 6.3.2 for additional details on dosing.

Therapeutic Individualization

The dosage including infusion rate should be individualized based on the clinical needs of the patient for both indications. The dosage is adjusted based on serum phosphorus, and clinical status. Monitoring of serum phosphorus 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.

6.3. 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, and the concentration of both erythrocyte adenosine triphosphate (ATP) and 2,3 diphosphoglycerate (DPG), and must be deemed as important to other tissue cells.

Pharmacokinetics of Phosphorus

Distribution

Approximately 85% of serum phosphorus is free and ultra-filterable and 15% is bound to protein.

Elimination

Intravenously infused phosphates not taken up by the tissues is 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

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The effectiveness of POTASSIUM PHOSPHATES INJECTION, USP, phosphorus (45 mmol/15 mL (3 mmol/mL) and potassium 71 mEq/15 mL (4.7 mEq /mL), in intravenous fluids to correct hypophosphatemia and as a source of phosphorus in parenteral nutrition (PN) for adult and adolescent 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 bio-bridge.

The LD has established safety and effectiveness in pediatric patients (neonates, infants, children, and adolescents) to correct hypophosphatemia and in PN (Prescribing information, Sodium phosphate injection, 2018). (b) (4) . Refer to Section 5.2.1 and Section 13.

For the PN indication, POTASSIUM PHOSPHATES INJECTION, USP is recommended in adults weighing at least 45 kg and pediatric patients 12 years of age and older weighing at least 40 kg due to the concern of risks of aluminum toxicity associated with the currently proposed formulation. In addition, to have a consistent pediatric population definition for both indications in minimizing the risk of dosing errors, the Applicant's proposal to recommend

POTASSIUM PHOSPHATES INJECTION, USP for correction of hyperphosphatemia in adults and pediatric patients 12 years of age and older is reasonable.

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

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 and the dosing recommendations are based on the LD, and the published literature.

To Correct Hypophosphatemia

The recommended phosphorus doses of the proposed product for an initial or single dose, ranging from 0.16 to 0.64 mmol/kg of phosphorus and dependent on serum phosphorus concentrations in the patients (Table 2), are derived from the available literature (See Section 8.1.5).

It has been reported in the literature that phosphates can be safely administered intravenously (IV) at initial doses of 0.2 to 1 mmol/kg of phosphorus in hypophosphatemic adults with normal blood calcium concentration and renal function. 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 maximum single dose of phosphorus is 45 mmol (potassium 71 mEq).

For peripheral administration, the maximum concentration for peripheral administration is phosphorus 6.4 mmol/100 mL (potassium 10 mEq/100 mL). Depending on the patient's needs, a central venous catheter may be used for higher concentration and the proper dilution of the product should follow.

Because of potassium can cause hyperkalemia, the infusion rate of the proposed product is also dependent on potassium in the recommended maximum dose. It has been reported that fast infusion of potassium is associated with chemical phlebitis and other potential adverse effects, including electrolyte disturbances and end-organ dysfunction.

For the intravenous administration of potassium, an infusion rate up to 10 mEq/hour potassium by peripheral line (6.4 mmol/hour of phosphorus for the proposed product) is generally recommended by practice guidelines. In cases where a higher infusion rate (> 6.4 mmol/hour) for phosphorus is needed that would exceed the infusion rate for potassium (i.e., 10 mEq/hour for adults or 0.5 mEq/kg/hour for pediatric patients), a central line should be used with continuous electrocardiographic (ECG) monitoring and monitoring of serum potassium concentrations.

The recommended dosage for pediatric patients 12 to <18 years of age is the same as that in adults. This recommendation is supported by the same daily requirement of phosphorus in

adults and children age 4 and older (Table 5) and there appears to be no differences in the physiology of phosphorus or the disease manifestations between adults and pediatric patients.

Parenteral Nutrition

The recommended dosage, 20 to 40 mmol/day of phosphorus in both adults and pediatric patients, is supported by the literature. Some patients may require higher or lower dosage depending on individual needs of patients.

The acceptable minimum body weight limits of 45 kg (adults) and 40 kg (pediatric patients), along with the maximum daily phosphorus doses of 45 mmol and 40 mmol, respectively, are recommended for these two patient populations, due to the risk of aluminum toxicity with the current proposed product. According to the regulations on aluminum in parenteral PN use, it is required for PN not to exceed the maximum daily aluminum exposure of 4 to 5 mcg/kg/day (65 FR 4103) to avoid the risk of aluminum toxicity. Refer to Section 5.2.1.

In the pediatric population 12 years of age or older, the average body weight of approximately 40 kg for children 12 to 13 years old represents the low end of the body weight in this population. The Applicant's aluminum content/specification is 15,000 mcg/L for the proposed product. Therefore, to ensure that the aluminum exposure from the proposed product is no more than 5 mcg/kg/day across the entire patient population, a maximum daily dose of 40 mmol along with the minimum body weight of 40 kg is conservatively recommended for pediatric patients 12 years of age and older. The aluminum exposure would be 5 mcg/kg/day for patients who receive 40 mmol/day and weigh 40 kg.

In adults, the body weight could be as low as approximately 45 kg. Since the Applicant's aluminum content/specification is 15,000 mcg/L for the proposed product, a maximum daily dose of 45 mmol along with the minimum body weight of 45 kg is conservatively recommended to ensure that the exposure to aluminum from the proposed product is no more than 5 mcg/kg/day across the entire adult patient population. The aluminum exposure would be 5 mcg/kg/day for patients who receive 45 mmol/day and weigh 45 kg.

Refer to Section 8.1.5 for additional details on dosing discussions.

Dosing consideration for Safety of Potassium

It is known that rapid dosing of potassium-containing products can cause significant morbidity and mortality. Hyperkalemia, which is an elevation from the normal potassium levels of 3.5-5.0 mEq/L, has significant clinical consequences. 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.

In addition, the recommended infusion rates of phosphorus not exceeding 6.4 mmol/hour via a peripheral line in an unmonitored patient would limit the potassium infusion rates to 10

mEq/hour, are acceptable and consistent with current clinical practice guidelines for potassium use.

Furthermore, in general, the proposed product will be administered in intravenous fluid to correct hypophosphatemia only when the baseline serum potassium is <4.0 mEq/L. An alternative source for parenteral phosphate such as sodium phosphate product should be used for patients with a serum potassium level ≥4 mEq/L.

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

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

Renal Impairment

There were no PK 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, the 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 concentrations.

The proposed product is contraindicated in patients with severe renal impairment or end stage renal disease (eGFR <30 mL/min/1.73 m^2) because of the risk for hyperphosphatemia and hyperkalemia. Refer to Section 8.2.4.9 - Use in Renal Impairment.

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.

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 as a source of phosphorus.

There were no clinical studies conducted for the drug-drug interactions. Nevertheless, 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 followings are the drug classes that can increase serum potassium concentrations by affecting the potassium homeostasis.

- Potassium-sparing diuretics such as amiloride, triamterene, and the spironolactones can increase potassium retention by reducing renal elimination of potassium and hence can produce severe hyperkalemia (Horisberger and Giebisch 1987).
- Renin-angiotensin-aldosterone system (RAAS) 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 that may result in important clinically relevant pharmacodynamic drug-drug interactions in the labeling is recommended.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant did not perform clinical studies; this review is literature-based and relies on the Agency's finding of safety and effectiveness for the LD (SODIUM PHOSPHATES INJECTION, USP). The Applicant initially submitted 51 references (see list in Section 15.1), but no clinical efficacy or safety summary, or clinical pharmacology summary. An IR was sent prior to filing and the requested summaries with references to the provided literature were provided.

7.2. Review Strategy

The Applicant supplied a list of references but presented no information about the methods used to identify these specific references. The Division of Epidemiology I (DEPI I), Office of Surveillance and Epidemiology Review (OSE), Office of Pharmacovigilance and Epidemiology (OPE) assessed the literature presented in this NDA to support the safety or efficacy of POTASSIUM PHOSPHATES INJECTION, USP, and performed an independent literature search and review. Despite the lack of specified methodology for the Applicant's literature search, DEPI concluded that the nine literature articles presented 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." DEPI also directed DGIEP to additional literature available to support pediatric dosing and phosphorus supplementation in PN (Wilson 1982, Table 7) however, noted there were no clinical trials performed in pediatric patients. See the DEPI review in DARRTS dated 08/21/2019 for an explanation of the methods used to assess the Applicant's literature search and for DEPI's complementary literature search.

Of the references identified by the Applicant, 9 clinical studies were cited for adults that evaluated intravenous potassium phosphates dosing and administration algorithms for the treatment of hypophosphatemia.

All the submitted articles presented in NDA 212121 are regarded as a reasonably complete representation of literature evidence available for POTASSIUM PHOSPHATES INJECTION, USP for the treatment of hypophosphatemia and use of potassium phosphate injection in PN in adults. Upon complete review of available literature, it was determined that the 9 articles identified by the Applicant represent the best available evidence to support the safety and efficacy of intravenous potassium phosphates to treat hypophosphatemia in adults. These 9 articles reporting on clinical trial data are summarized below in Section 8.1 and Table 5. DEPI's PubMed search identified additional articles that provide support to the adult and pediatric indication for correction of hypophosphatemia and use in PN; these are summarized in Table 7 in Section 8.1.

Section 8.1 also contains a dosing discussion for pediatric patients (Section 8.1.4), for both correction of hypophosphatemia (Section 8.1.5) and PN (Section 8.1.6).

Table 5 and Table 7 summarize the efficacy and safety literature considered in this review.

8. Clinical Evaluation

8.1. Review of Evidence Used to Support Efficacy

8.1.1. Reference Listed Drug (RLD)

The proposed product is relying upon the Agency's findings of safety and efficacy for Sodium Phosphates NDA 018892), approved in 1983. The Applicant is proposing the same indications for which NDA 018892 was approved. SODIUM PHOSPHATES INJECTION, USP is currently marketed by Hospira, Inc. and has not been withdrawn due to reasons of safety or effectiveness.

8.1.2. Integrated Assessment of Effectiveness – Published Literature

Overall, there are a few clinical trials that investigated the clinical outcomes associated with intravenous replacement of phosphorus, including during PN. These trials were open-label in design using biomarker changes as endpoints; specifically, the patients' baseline serum phosphorus level was the comparator, and post-treatment serum phosphorus levels a marker of treatment response. Safety outcomes based on assessment of serum calcium, magnesium and potassium levels were reported (See Section 8.2 - Review of Safety). Available published clinical trials were conducted under widely varying conditions, and datasets and case report forms (CRFs) from these trials are not available for detailed review.

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 and is generally higher in children:

In males, the reference range is as follows:

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

In females, the reference range is as follows:

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

The provided literature evidence demonstrates that serum levels of phosphorus increased in hypophosphatemic patients who received intravenous potassium phosphates. In general, the studies showed that the lower the baseline serum phosphorus levels were, the higher the dose of phosphates required to achieve a post-treatment level in the normal reference range (Table 5 and Table 7 for Summary Literature Review). 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. In general, there is no established maximal daily dose of phosphorus, as phosphorus should be repleted until normal serum levels are obtained and sustained. However, there is literature that supports a maximum initial or single dose of 45-50 mmol phosphorus in adults, followed by repeat assessment of the patient, and obtaining serum phosphorus, potassium and calcium levels prior to repeat doses (Shackney and Hasson 1967). The total daily dose of potassium phosphates is limited by the maximal recommended daily dose of potassium, which is generally 200 mEq daily. However, more can be required in severely hypokalemic patients.

Adequate information has been provided to support the dose and efficacy of POTASSIUM PHOSPHATES INJECTION, USP in adults and children for the indication of correction of hypophosphatemia and for use in PN from the LD and the referenced literature (Table 5 and Table 7). The safety of POTASSIUM PHOSPHATES INJECTION, USP in both adults and pediatric patients is supported by the referenced literature (Table 5 and Table 7).

The dose of this product for use in PN is limited by the aluminum content of this product (see Section 8.2.4.8, Aluminum Content of Drug Product), and is therefore restricted to 45 mmol daily in adults weighing at least 45 kg and to 40 mmol daily in pediatric patients 12 years and older weighing at least 40 kg, to comply with the CFR 201-323 requirements that total aluminum exposure not exceed 5mcg/kg/day in products used in parenteral nutrition.

Table 4. Recommended Daily Allowance/Intake

Nutrient	Unit of measure	RDI			
		Adults and children =4 years	Infants 1 through 12 months	Children 1 through 3 years	Pregnant women and lactating women
Phosphorus	Milligrams (mg	1,250	275	460	1,250

[1]RDIs are based on dietary reference intake recommendations for infants through 12 months of age.
Source: 21 CFR 101

The literature supports the recommendations to assess serum calcium, magnesium and potassium levels, along with other serum electrolytes, prior, during, and following dosing of potassium phosphates and to use only in patients with a serum potassium level of <4 mEq/dL to minimize the risk for hyperkalemia. It is also important to normalize serum calcium levels prior to infusion of phosphates. 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. (See Section 8.2, Safety Review Approach)

Table 5 below describes data from the nine clinical trial publications that were submitted by the Applicant in support of the indications for:

> **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 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.

Table 7 below provides a summary of additional articles that support the efficacy and safety for this indication. These articles were not initially submitted by this Applicant; however, they were identified from the PubMed search performed by DEPI.

Table 5. Summary of Published Clinical Trial Data to Support Efficacy and Safety of Potassium Phosphates in Intravenous Fluids to Correct Hypophosphatemia or as a Source of Phosphorus in PN (Submitted by the Applicant)

Reference	Design/Drug	Population	Doses/Duration[10]	Outcomes	Complications/AEs
Vanetta 1981)	Open-label, prospective KH_2PO_4	10 adults with phosphorus P[1]) ≤1 mmol/dL, normal or low K^{+2} and no RI[3]	9 mmol P q12h up to 48h; Ca^+4, P and K^+ measured q12h	All pts responded, with P >1 mg/dL at 36 hours and normal in 6 pts at 48 hours	1 with hyperP, 1 patient pt) with decreased Ca^+ asymptomatic 8 pts with low Mg^{+5}
Vanetta 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 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 48 h post-treatment serum Ca^+ levels below 8.5 mg/dL range 7.0-8.3) in 7 of 10 pts; however, 6 of these 7 pts had pre-treatment serum Ca <8.5 mg/dL. All patients 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	10-15 mmol P mean 0.3 mmol/kg over 4 hours ; range 0.19-0.8 mmol/kg over 4 hours	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^+ One patient 3%) “showed transient deterioration in renal function in the two days after phosphorus infusion and this may have been due to septicemia.” No significant change in the mean serum Ca^+

Reference	Design/Drug	Population	Doses/Duration[10]	Outcomes	Complications/AEs
Clark 1995)	Open-label Prospective ICU sodium or potassium phosphates	78 adults <u>on PN</u>, P <3 mg/dL, no RI, no obesity, normal Ca+	•<u>mild</u> 2.3 to 3 mg/dL - 0.16 mmol/kg •<u>mod</u> 1.6 to 2.2 mg/dL - 0.32 mmol/kg •<u>severe</u> <1.5 mg/dL - 0.64 mmol/kg In 100 cc over 4-6 hours **single dose** P, Ca^+, Mg^+, albumin, BUN, creatinine measured daily x 3d	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
Rosen 1995)	Open-label, prospective ICU sodium or potassium phosphates	11 adults, P <2 mg/dL, normal Ca^+, not pregnant or BF[6]; excluded creat clearance <10 mL/min, creatine >4, BUN >80, u/o[7] <30ml/h	15 mmol P over 2hours, K+P[8] if K^+ ≤3.5 mg/dL, NaP[9] if K^+ >3.5 mg/dL 2nd dose if P <2 mg/dL at 6 hours, 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 1 dose	No clinically significant adverse events No significant changes noted in serum calcium, magnesium or potassium concentrations, urine output, vital signs, or reflexes

Reference	Design/Drug	Population	Doses/Duration[10]	Outcomes	Complications/AEs
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 2 hours or 30 mmol over 4 hours Severe - <1.2 mg/dL either 45 mmol over an hour or 45 mmol over 6 hours	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 24 hr in 28%

Reference	Design/Drug	Population	Doses/Duration[10]	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,	See Table 6 below. Dosed in IV fluids	Retrospective – Success in P repletion: 53% in moderate pts 27% in severe pts Prospective – 84 76%) reaching normal P after a 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 patients 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/L and NaP used if K ≥4 mEq/L; up to two daily doses, infused at ≤7.5 mmol/hour.	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

1 - P – phosphorus
2 - K^+ - potassium
3 - RI – renal insufficiency
4 - Ca^+ - calcium
5 - Mg^+ - magnesium
6 – BF - breast feeding
7 – u/o – urine output
8 – K+P – potassium phosphates injection
9 – NaP - sodium phosphates injection
10 – normal references ranges used for phosphorus were not specified in these articles

Table 6. Phosphorus Repletion Protocol for Taylor 2004 Trial

Phosphorus level	Weight 40–60 kg	Weight 61–80 kg	Weight 81–120 kg
<1.0 mg/dL	30 mmol Phos IV	40 mmol Phos IV	50 mmol Phos IV
1.0–1.7 mg/dL	20 mmol Phos IV	30 mmol Phos IV	40 mmol Phos IV
1.8–2.2 mg/dL	10 mmol Phos IV	15 mmol Phos IV	20 mmol Phos IV

Source: article Table 1.
If the patient's potassium is <4.0 use potassium phosphorus;
If the patient's potassium is >4.0 use sodium phosphorus. IV, intravenous;
Phos phosphorus.

Table 7. Additional Literature to Support Efficacy and Safety of Potassium Phosphates in Intravenous Fluids to Correct Hypophosphatemia

Reference	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 3-5 days. Group B: all 5 pts hypoP in 1-7 days Groups 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 calories. 14-17 mmol phos/1000cal
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 8 hours	Mean left ventricular stroke work for these patients increased from 49.57 to 71.71 g-m per beat P<0.01)		Improved cardiac output with P normalization

Reference	Design/Drug	Population	Doses	Outcomes	Complications	Comments
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 included both adults and peds pts	Not given P [N 15] 15 mmol Na+P [N 17] 15 mmol Na+P X 3 doses [N=15]	Measurements at 24 hours 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 $_2$D r -0.62, P<0.005)		No significant change in [Ca] or [Mg]
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 12-14 hours [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
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

Source: Reviewer Table

8.1.3. Studies to Support Efficacy and Safety of Potassium Phosphates in Patients Receiving PN

The Applicant submitted several literature references that used phosphorus injection in PN, with both the potassium salt and sodium salt. Clark 1995 (Table 5) reported on a graduated dosing for hypophosphatemia in patients receiving PN. Brown 2006 and Charron 2003 (Table 5) also did studies on patients receiving PN. Pigon 1985 reported on using phosphates in PN (Table 7). Taylor 2004 (Table 5) reported on 111 patients with hypophosphatemia receiving PN and phosphorus repletion. Brown also treated 79 patients with hypophosphatemia on PN. In most of these studies for hypophosphatemia, the phosphorus was not added to the PN but given separately, though in two of the studies, the patients received both phosphorus in the PN and additional phosphorus replacement in IV fluids.

Sheldon and Grzyb (1975) reported on a study to maintain normal serum phosphorus levels in patients receiving PN and stated, "Provision of 20 to 25 mEq of potassium dihydrogen phosphate per 1,000 K Calories will maintain normal serum levels of inorganic phosphate during total parenteral nutrition."

There was no literature submitted with clinical trial data for pediatric patients receiving PN.

8.1.4. Pediatric Efficacy Literature Review

See Section 10, Pediatrics.

No clinical trials in pediatric patients were found in the literature search. The search conducted by DEPI found "very limited information" in children. Five articles about the frequency of hypophosphatemia in acutely or critically ill children were reviewed for data (Antachopoulos et al. 2002; de Menezes et al. 2006; Santana e Meneses et al. 2009; Kilic et al. 2012; Rady et al. 2014). None of these articles provided additional meaningful clinical evidence about treating children with intravenous potassium phosphates. However, the LD, sodium phosphates, is approved for all ages, which supports the efficacy and safety of phosphorus use in pediatric patients.

The efficacy and necessity of maintaining normal serum phosphate 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; Mihatsch et al. 2018).

See Section 8.1.6 for a discussion of the dosing of potassium phosphates in PN.

8.1.5. Discussion of Dosing for Treatment of Hypophosphatemia

See Table 5,

Table 6 and Table 7 above.

In adults with hypophosphatemia with normal blood calcium concentration and functioning kidneys, medical literature, textbooks, and review articles indicate that phosphorus can be

safely administered intravenously as sodium or potassium phosphates salts at initial doses of 0.2–1 mmol/kg of phosphorus, appropriately diluted and at appropriate rates, with close monitoring of phosphorus and calcium levels throughout treatment (Felsenfeld and Levine 2012; Bringhurst et al. 2018).

The dosage of phosphates should be based on the patients' clinical condition, symptoms of hypophosphatemia and baseline serum phosphorus level. The dosing chart (see Table 2) from the Division's recommended labeling indicates the recommended doses that were derived from the available literature for the correction of hypophosphatemia. Close monitoring of serum phosphorus, calcium, magnesium and potassium are necessary prior to, during and after treatment.

The Applicant proposed (b) (4) [redacted] (b) (4) [redacted] (b) (4) [redacted] Therefore, the dose should be calculated based on the patient's weight[7] and baseline serum phosphorus level (see Table 2), with a maximum initial or single dose of 45 mmol of phosphorus. Serum phosphorus, potassium, calcium levels and the patient should be reevaluated prior to repeat dosing. It may take several doses to correct severe hypophosphatemia; hypophosphatemia can reoccur as phosphorus shifts into the intracellular space. Refeeding hypophosphatemia can also occur with the initiation of PN.

In general, unless the patient has an underlying disease that causes phosphorus wasting (such as Falconi's syndrome) several doses over a few days are adequate to restore normal serum phosphorus levels. At that time, if the patient still cannot tolerate oral feedings, usually PN will be instituted and the patient will receive phosphorus maintenance doses in the PN.

There are no regulations limiting aluminum exposure in non-PN products; however, the Applicant-requested pediatric age limitation for both indications has been included as part of

[7] Limited information is available regarding dosing of patients significantly above ideal body weight; consider using an adjusted body weight for these patients.

the hypophosphatemia indication at the Applicant's request due to decrease the risk for dosing errors (See Sections 8.1.5, 8.1.6 and 11 and Table 2.)).

When administering potassium phosphates, the baseline serum potassium level should be assessed and in general, potassium phosphates should not be used in patients with serum potassium levels >4.0 mEq/L.

Rate of Administration

The maximum rate of infusion of POTASSIUM PHOSPHATES INJECTION, USP is limited by the amount of potassium and phosphorus in the solution and the concentration of the solution.

The maximum recommended infusion rate in adults via a peripheral line should generally not exceed 6.4 mmol/hour of phosphorus (10 mEq/hour of potassium). Higher rates can cause chemical phlebitis. This recommendation is based upon extensive clinical experience and general practice guidelines, based on scientific literature, for the administration of potassium.

In adult cases of 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 electrocardiographic (ECG) monitoring and monitoring of serum potassium concentrations. Faster rates of infusion have resulted in calcium phosphate precipitates leading to hypertension, pulmonary embolism and acute renal failure and other potential adverse effects including electrolyte disturbances and end-organ dysfunction (Shackney and Hasson 1967).

In pediatric patients 12 years of age and older, an infusion rate of more than 3.2 mmol/kg/hour of phosphorus (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).

The maximum concentration of the injection solution should be phosphorus 18 mmol in 100 mL (potassium 28.2 mEq/100 mL) of intravenous fluids. Due to the risk for calcium phosphorus precipitation, avoid infusion with calcium-containing products except in PN.

Dosing Recommendations in Pediatric Patients Age 12 years and older

Normal serum phosphorus concentrations are higher in children, and thus, reference range cutoff values for children will be higher. Hypophosphatemia in children 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 children.

There appear to be no key fundamental differences between adult and pediatric populations in the manifestations of hypophosphatemia. The physiology of phosphorus repletion also appears to be essentially the same in both populations.

In general, for pediatric patients age 12 to <18 years, the dosage for repletion of phosphorus should be the same as that in adults when considering daily phosphorus requirements, as children age 4 and older have the same RDA/RDI as adults (21 CFR 201.101).

While the FDA does not regulate aluminum exposure in non-PN products, the Applicant has requested a deferral for the pediatric assessment of this product in pediatric patients less than 12 years of age, as aluminum exposure in this pediatric subpopulation could potentially exceed the allowable amount (See Section 5 and Section 8.2.4.8). The Applicant has agreed to (b) (4) by December of 2020 under a PREA PMR to reduce the aluminum content to a level acceptable for all ages (See Section 13).

8.1.6. Dosing in Total Parenteral Nutrition (PN)

Adult Dosing With PN

Potassium phosphates dosing in PN also needs to be individualized to the patient's needs. The patient's underlying clinical condition, nutritional requirements, and the contribution of oral or enteral phosphorus and potassium intake. Serum phosphorus, potassium, calcium and magnesium concentrations should be monitored. The phosphorus added to PN is limited by the calcium also present in PN and thus, the amounts given in PN are for maintenance of normal phosphorus levels. The phosphorus in PN is not usually given to correct hypophosphatemia. The available literature supports a dose of approximately 14 to 17 mmol/1000 calories of potassium phosphates in PN to meet daily dietary requirements and prevent hypophosphatemia in adults. This recommendation is consistent with the approved sodium phosphate labeled dose for PN (12 to 15 mmol/250 grams of dextrose or 850 calories) and consistent with the RDA/RDI and current clinical experience and practice guidelines that are supported by the reference literature provided (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). The LD's recommendation does not distinguish between adults and pediatric patients 12 years and older; the only age subgroup with a distinct dosing recommendation is infants.

In adults and pediatric patients 12 years of age weighing at least 40 kg, the generally recommended dosage for phosphorus in PN is 20 to 40 mmol/day in parenteral nutrition. See discussion in the following section of how the LD dosage regimen for patients of all ages beyond infancy equates to the recommended dosage regimen for POTASSIUM PHOSPHATES INJECTION, USP in adults and pediatric patients 12 years of age weighing at least 40 kg.

The maximum dosage of this formulation of POTASSIUM PHOSPHATES INJECTION, USP is phosphorus 45 mmol/day (potassium 71 mEq/day) for adults weighing at least 45 kg and phosphorus 40 mmol/day (potassium 63 mEq/day) in pediatric patients 12 years of age or older and weighing at least 40 kg, based upon the aluminum content of the product. The low end of the dosage range should be utilized in patients with moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2).

Pediatric Dosing With PN

In pediatric patients 12 to <18 years of age and weighing at least 40 kg, the recommended maintenance dosage is approximately 20 to 40 mmol/day of phosphorus. As in adults, requirements may be higher or lower depending on individual needs (Sheldon and Grzyb 1975; Pigon et al. 1985; Greene et al. 1988; Mirtallo et al. 2004; Felsenfeld and Levine 2012; McClave et al. 2016; Mihatsch et al. 2018; American Society for Parenteral and Enteral Nutrition (ASPEN) 2019).

These dosage recommendations for adolescent patients 12 years of age and older are in alignment with the literature reviewed, and current clinical experience and guidelines derived from the literature presented (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).

- Per ASPEN guidelines: Adolescents and children greater than 50 kg: 10-40 mmol daily

The Sodium Phosphate Injection PI (in the Clinical Pharmacology section) states: “It has been suggested that patients receiving total parenteral nutrition receive 12 to 15 mmol phosphorus per 250 g of dextrose.”

1 gram of dextrose = 3.4 calories

250 grams dextrose = 850 calories

Therefore, 14 to 18 mmol phosphorus/1000 calories.

This is consistent with the literature (Sheldon 1975, Annals of Surgery, p 683-689).

Assuming a typical diet of 2500 calories, this equated to a 20 to 40 mmol/day phosphorus dosage for an adult or adolescent.

The Applicant proposed a dose for PN (b) (4); however, since the product is limited to age 12 and above, and these pediatric patients have the same requirement as adults, the review team determined that a simplified dosing recommendation was appropriate.

The maximum dose is limited by the aluminum content of the product for use in PN and will be 40 mmol of phosphorus in pediatric patients 12 years of age and older weighing at least 40 kg.

(b) (4)

8.2. Safety Review Approach

The safety review for intravenous potassium phosphates is based on the literature and information from the clinical trials performed and reviewed in detail above. See Table 5, Table 7, Table 8, and Table 9, summarizing the safety results from the literature review. Additional

literature about the safety of potassium phosphates infusions and the aluminum content of the proposed product is detailed below.

8.2.1. Review of the Safety Database

Overall Exposure

No clinical trials were performed by the Applicant. This NDA relies on the FDA's findings of safety from the LD, SODIUM PHOSPHATES INJECTION, USP (NDA 018892), as well as the literature that supports the safety of and dosing with respect to the potassium salt. Thirteen publications were submitted to support safety results from 8 U.S. (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) and 5 non-U.S. (Kingston and Al-Siba'i 1985; Pigon et al. 1985; Perreault et al. 1997; Charron et al. 2003; Bech et al. 2013) clinical studies of 526 adults, including 511 adults treated with intravenous potassium phosphates. See Table 5, Table 7, Table 8 and Table 9.

8.2.2. Adequacy of the Safety Database

See above Sections 8.1.1 and 8.1.2. The safety of the historical and current clinical use of potassium phosphates relies on the LD, and is demonstrated through published literature, including current practice guidelines, which are supported by the published literature (Greene et al. 1988; Mirtallo et al. 2004; Mihatsch et al. 2018; American Society for Parenteral and Enteral Nutrition (ASPEN) 2019). The data are determined to be adequate to assess the safety and inform the labeling.

Issues Regarding Data Integrity and Submission Quality

No clinical trials were performed; however, the LD and literature-based application was acceptable for filing and review under the 505(b)(2) pathway.

QT

The DCRP QT review stated that, "A TQT study is not needed per ICH E14 because the doses for potassium and phosphate are not higher than approved products on US market."

8.2.3. Summary of Safety Results from Literature Review

See Table 5 and Table 7 above for the summary of adverse events and complications associated with repletion of hypophosphatemia. See also Table 8 and Table 9 below for additional articles with adverse events reported. See also Section 8.2.4 - Analysis of Submission-Specific Safety Issues.

Intravenous potassium phosphates are contraindicated in patients with hyperkalemia, hyperphosphatemia, significant hypocalcemia and severe renal impairment or end stage renal

disease. Note that most studies excluded patients with renal impairment and other co-morbidities. Except for the study by Perreault (1997) and Kingston (1985) (Table 5).

Hyperphosphatemia occurred with the higher doses of potassium phosphates in the publications reviewed (e.g., 1 mmol/kg). The dose should be individualized to the patients' clinical condition, risk for significant total body depletion of phosphorus and clinical signs or symptoms. In general, it is prudent to recheck serum phosphorus levels frequently (e.g., after infusing an initial recommended dose and after each subsequent dose. (See Sections 8.1.5 and 11) in patients with severe hypophosphatemia.

Hyperkalemia was also reported in several of the publications reviewed with administration of potassium phosphates. In general, use of potassium phosphates should be limited to patients with a serum potassium level of < 4.0 mEq/L at baseline to minimize the potential risk for hyperkalemia. Sodium phosphates injection can be used as an alternative in patients with serum potassium ≥4.0.

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

Hypomagnesemia was commonly reported in association with hypophosphatemia, and can be a result of phosphorus administration. See Section 8.2.4.7.

Table 8. Literature Reviewed With Adverse Reactions to Sodium or Potassium Phosphates Injections

Author Year	Submitted With NDA	Not Submitted	Brief Summary Prepared by DEPI
Shackney 1967)	X		**Shackney 1967** reported two cases of hypotension and renal failure leading to death in patients treated with 50-100 mmol P IV for high Calcium.
Zipf 1979)	X		After observing one case of symptomatic hypocalcemia with hyperphosphatemia, **Zipf 1979** prospectively assessed seven children age 9-17 years with diabetic ketoacidosis managed with potassium phosphate IV.
Winter 1979)	X		**Winter 1979** described one case of hypomagnesemia, hypocalcemia, and hyperphosphatemia attributed to potassium phosphates IV in a 9-year-old boy with diabetic ketoacidosis.
Chernow 1981)		X	**Chernow 1981** described 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)		X	**Wetherton 2003** presented four cases of in-hospital death associated with accidental intravenous administration of potassium chloride or potassium phosphate N=1, 26.4 mmol push, age 81 years .
Felton 2006)		X	**Felton 2006** described clinical deterioration in a 43-year-old septic patient 90 minutes after the sequential intravenous administration of calcium gluconate and potassium phosphates.

Source: Table 7 from DEPI review by Joel Weissfeld

8.2.4. Analysis of Submission-Specific Safety Issues

8.2.4.1. Review of Literature to Support Safety of Potassium Salt and Potassium Dose for Addition to Intravenous Fluids to Correct Hypophosphatemia

Normal potassium level in the blood is 3.5-5.0 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. Therefore, while the active ingredient is phosphate, the administration of potassium phosphates must consider the dose of potassium being co-administered as part of the active ingredient of the product. 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 >4.0 mEq/L should not be treated with potassium phosphates products and should alternatively receive a sodium phosphates product secondary to the increased risk for treatment-related hyperkalemia (Hemstreet et al. 2006). Patients with severe renal impairment and end stage renal disease (ESRD) should also not receive the potassium phosphates product due to 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.

The maximum dose noted in the labeling for the indication 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 is 0.64 mmol/Kg of phosphorus. This would result in a dose of 71 mEq/Kg of potassium. This dose is less than the suggested maximum potassium daily dose in other potassium-containing products used as a source of potassium; however, as the dose for correction of hypophosphatemia, the maximum age-adjusted daily dose for potassium should not be exceeded. For the PN indication, the maximum daily dose is 45 mmol phosphorus (71 mEq potassium) for adults and 40 mmol phosphorus (63 mEq potassium), and would by itself not exceed the daily potassium dose, however, the potassium content of other products will need to be taken into consideration.

The labeling states that when administering POTASSIUM PHOSPHATES INJECTION, USP in intravenous fluids to correct hypophosphatemia, check the serum potassium concentration prior to administration. If the potassium concentration is 4 mEq/dL or more, do not administer the product and an alternative source of phosphate should be used instead. The choice of administration through a central or peripheral venous catheter is dependent upon the concentration of the diluted solution. A generally recommended maximum concentration for peripheral administration is phosphorus 6.4 mmol/100 mL (potassium10 mEq/100 mL). The recommended infusion rate is approximately phosphorus 6.4 mmol/hour (potassium 10 mEq/hour). Continuous electrocardiographic (ECG) monitoring is recommended for higher infusion rates of potassium, i.e., more than 10 mEq/hour in adults and 0.5 mEq/kg/hour in pediatric patients 12 years of age and older.

Table 9. Publications Supporting Safety of Potassium Administration as Potassium Chloride

Author Year	Brief Summary
Singhi 1994)	Administered concentrated potassium chloride 200 mmol/L [200mEq/L]) at 0.25 mmol/kg/hour to 20 hypokalemic children.
Kruse 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.

Source: Reviewer table

Conclusion

When diluted and administered at the appropriate rate with appropriate monitoring and at the labeled dose, the potassium content of this product is safe.

8.2.4.2. Risk of Pulmonary Embolism Secondary to Pulmonary Vascular Precipitates

Please see the review by DEPI filed under NDA 020678 and 020734, July 2, 2013 regarding risk of pulmonary vascular precipitates (PVP) 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.

The labeling will reflect a maximum initial or single dose of 45 mmol phosphorus for treatment of hypophosphatemia, and a maximum rate via a peripheral venous catheter of 6.4 mmol/h and 15 mmol/h via a central venous catheter to prevent precipitation. Maximum concentrations of the solutions have also been specified in the labeling (See Section 11). There is also a contraindication for use in patients with hypercalcemia, to prevent calcium-phosphate precipitation.

8.2.4.3. Serious Cardiac Adverse Reactions with Undiluted, or Bolus or Rapid Intravenous Administration

Rapid administration of products containing potassium can cause cardiac arrhythmia (including QT prolongation), cardiac arrest, seizures, muscle spasms and death. This product must be diluted in appropriate amounts of intravenous fluid or parenteral nutrition and administered at no more than the maximum rate indicated in the labeling (see Section 8.1.5 - Discussion of Dosing for Treatment of Hypophosphatemia and Section 8.2.4.11 and Section 8.2.7 - Additional Safety Explorations).

QT Assessment

See the CDER Division of Cardiovascular and Renal Products (DCRP) QT Interdisciplinary Review Team memorandum by Christine Garnett, Pharm.D., Clinical Analyst, dated June 11th, 2019 in DARRTS.

The DCRP QT review stated that, "A TQT study is not needed per ICH E14 because the doses for potassium and phosphate are not higher than approved products on US market."

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 and another admitted for chronic alcoholism and pneumonia after administration of intravenous potassium phosphates. The adverse events described in these case reports were associated with very large infusions of potassium phosphates daily (approximately 115-170 mmol phosphate per day which is higher than the recommended maximum dosage for a single or initial dose in the prescribing information 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

Three publications were identified by DPV of original data reporting new onset hypomagnesemia following potassium phosphates injection. Intravenous potassium phosphates were used to treat hypercalcemia of malignancy in adults in one publication

(Fulmer et al. 1972) and diabetic ketoacidosis (DKA) in children in two publications (Winter et al. 1979; Zipf et al. 1979). These data suggest that systemic acute administration of potassium phosphates may be associated with a decline in serum magnesium levels if: (1) the product is infused too rapidly or in excessive amount, thus causing calcium-phosphorus precipitate 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

An additional area of concern for POTASSIUM PHOSPHATES INJECTION, USP is the exposure of at-risk individuals to levels of aluminum that may be toxic. To limit the risk of aluminum toxicity, FDA modified its "Regulations on Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition" and enacted the Final Rule in July 2004 (65 FR 4103). The Final Rule requires that small volume parenteral products must state the maximum aluminum concentration at the time of product expiry on the product's label; and provide a package insert that includes 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 the toxicology review, the Applicant's maximum aluminum content/specification of 15,000 mcg/L is justified based on the maximum daily dose (MDD) of 45 mmol phosphorus (15 mL/day) in adult patients weighing at least 45 kg and 40 mmol phosphorus (13 mL/day) in pediatric patients 12 years of age or older weighing at least 40 kg for use in PN. 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 unapproved products currently on the market.

8.2.4.9. Use in Renal Impairment

Use in patients with severe renal impairment or end stage renal disease (eGFR <30 mL/min/1.73 m^2) 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.

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.

8.2.4.10. Use in Adrenal Insufficiency

In patients with severe adrenal insufficiency, administration of potassium phosphates may cause potassium intoxication secondary to hyperaldosteronism and impaired urinary secretion of potassium due to adrenal gland dysfunction. To avoid potassium intoxication, infuse potassium-containing solutions slowly and monitor by continuous electrocardiography (ECG). Serum potassium levels are not necessarily dependable indicators of tissue potassium levels (Biam et al. 1980).

8.2.4.11. Use in Cardiac Disease

Use with caution in the presence of cardiac disease, particularly in digitalized patients secondary to risk for hyperkalemia or hypocalcemia which can interfere with the action of digitalis (Taketomo 2017).

8.2.5. Safety Analyses by Demographic Subgroups

There is information available on pediatric and adults (See Section 8.2.3). There is no information on other demographic subgroups.

8.2.6. Specific Safety Studies/Clinical Trials

Not applicable.

8.2.7. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No information available.

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 (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 listed drug 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.

Pediatrics and Assessment of Effects on Growth

No information available.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Iatrogenic overdose of POTASSIUM PHOSPHATES INJECTION, USP is possible with resultant hyperphosphatemia, hyperkalemia and hypocalcemia. However, these can be avoided with proper dosage and avoiding use in patients with serum potassium <4 mEq/L or significant hypocalcemia.

Safety Concerns Identified Through Postmarket Experience

See Section 8.2.4.3 - Serious Cardiac Adverse Reactions with Undiluted, or Bolus or Rapid Intravenous Administration for discussion of the adverse event history from the unapproved marketed formulations of potassium phosphates and the approved sodium phosphates.

The Division of Pharmacovigilance I (DPV-I) completed a review, dated August 13, 2019, of all reports of adverse events associated with intravenous (IV) administration of potassium phosphates injection or SODIUM PHOSPHATES INJECTION, USP (i.e., the LD for this NDA) in the FDA Adverse Event Reporting System (FAERS) database through April 22, 2019. Furthermore, DPV-I evaluated adverse event reports that the Applicant provided as justification for the inclusion of the following terms in ADVERSE REACTIONS based on postmarketing data: (b) (4) . Of note, the ADVERSE REACTIONS section states that the events in this section occurred in patients receiving intravenously administered potassium phosphates within the recommended dosage range.

The search of the FAERS database identified 15 adverse event 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, and 1 involved usual use. The 14 cases involving improper administration of potassium phosphates injection 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 (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 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: bradycardia, cardiac arrest, hyperkalemia, hypotension, and cardiac arrhythmia (i.e., ventricular fibrillation).

Of 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 following terms are included in the proposed ADVERSE REACTIONS section of the IV POTASSIUM PHOSPHATES INJECTION labeling: cardiac arrest, dyspnea.

Of three FAERS cases of IV potassium phosphates overdosage, two had an outcome of death. These cases described patients who experienced hyperphosphatemia, muscles "locking up" (this case was coded with the MedDRA PT Muscle spasm), cardiac arrhythmia, or cardiac arrest after receiving IV potassium phosphates in the following manners: two adult patients, one of whom 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 received 273 mmol phosphates/400 mEq potassium over 3 hours and died, and one infant who received 17.4 mmol phosphates/25.5 mEq potassium over an unreported duration and died.

Of the terms that the Applicant proposed to include in ADVERSE REACTIONS based on postmarketing adverse event reports, the FAERS case series did not describe the following events with usual *or* inappropriate IV administration of potassium phosphates: (b) (4)

DPV-I reviewed the postmarketing reports that the Applicant provided as justification for these aforementioned terms and determined that these events were not possibly or probably associated with IV potassium phosphates administration, and some of the reports did not actually describe the proposed adverse event.

DPV-I completed a second review, dated September 11, 2019, which contained an evaluation of the medical literature for an association between hypomagnesemia and potassium phosphates injection. 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 diabetic ketoacidosis (DKA) in children(Winter et al. 1979; Zipf et al. 1979).

These uncontrolled case series and reports suggest that systemic acute administration of potassium 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

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. The available evidence, however, suggests the possibility that certain patients receiving potassium 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 ~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.

Expectations on Safety in the Postmarket Setting

Secondary to reports of inappropriate administration and medication errors, in 2006, an Institute of Safe Medicine Practice (ISMP) newsletter was published re: 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 FDA had received a report from one institution of two deaths and at least two cases of respiratory distress, which 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).

In 2013 a published an article “Reducing the risk of harm from intravenous potassium: A multi-factorial approach in the haematology setting.” This publication, 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. However, it is noted that CMP Development’s POTASSIUM PHOSPHATES INJECTION, USP contains 4.7 mEq of potassium/mL compared to 4.4 mEq of potassium/mL in the currently unapproved products. The difference in potassium content is relatively small, but the potassium content should be clearly labeled to help providers take this into account when ordering this new formulation.

8.2.8. Integrated Assessment of Safety

The safety of POTASSIUM PHOSPHATES INJECTION, USP is based upon published literature in adult patients with, or at risk for, hypophosphatemia, and the findings of safety (and effectiveness) for SODIUM PHOSPHATES INJECTION, USP (NDA 18-892). The safety of phosphates injection for pediatric patients is based upon the finding of safety and effectiveness of SODIUM PHOSPHATES INJECTION, USP. The safety of potassium phosphates in pediatric patients is also supported by the published literature on potassium administration. There were

no pediatric safety or efficacy studies of potassium phosphates injection for the treatment of hypophosphatemia identified in the literature. However, there was some literature supporting use of potassium phosphates in PN in pediatric patients. Most publications described studies with small sample sizes, in which subjects were placed into unblinded treatment groups, or were case reports. In some instances, both oral and parenteral phosphates were administered, or parenteral sodium and/or potassium phosphates were administered. Despite the limitations with the collection and description of adverse events in the published studies, there has been considerable postmarket experience with both intravenous potassium phosphates and sodium phosphates.

The safety of POTASSIUM PHOSPHATES INJECTION, USP is reviewed in Section 8.2, and it is noted that, given incorrectly, this product can be life-threatening. It is essential that POTASSIUM PHOSPHATES INJECTION, USP be properly diluted and given at a rate equal to or less than the maximum recommended rate and at the correct dose, and that the patient be monitored appropriately.

POTASSIUM PHOSPHATES INJECTION, USP is contraindicated in patients with ESRD, severe renal insufficiency, hyperkalemia, hyperphosphatemia, hypercalcemia or significant hypocalcemia.;

Precautions should be taken when administering POTASSIUM PHOSPHATES INJECTION, USP to patients with underlying cardiac disease or moderate renal impairment. Hyperkalemia, hyperphosphatemia, hypocalcemia and hypomagnesemia can all occur secondary to POTASSIUM PHOSPHATES INJECTION, USP.

In summary, adverse events and toxicities associated with potassium phosphates injection as reported from clinical studies, standard handbooks, published trials, case reports, and FAERS were consistent and rarely clinically significant within the recommended dosage range. However, there is significant potential for serious adverse events with inappropriate dilution, rapid administration or administration of an excessive dose. Several published case reports have documented serious adverse outcomes associated with infusion of large (50-170 mmol) quantities of phosphorus among children and adults over a range of 1 to 24 hours.

To avoid potassium or phosphorus intoxication, the safety data, while limited, support the common practice of infusing solutions containing potassium phosphates slowly. Major side effects are greater when intravenous phosphorus is administered to adults in doses of 50 mmol or more over 3 hours or less; therefore, a cautious rate of administration and limiting doses to less than 50 mmol has been recommended.

Infusing high concentrations of phosphorus may cause hypocalcemia and calcium levels should be monitored. 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.

For the use in PN indication, the Applicant claims that the aluminum levels in the proposed POTASSIUM PHOSPHATES INJECTION, USP product will be lower than those of the unapproved products. However, aluminum levels will not low enough to meet the exposure level of not more than 4-5 mcg/kg/day for all pediatric patients. With a proposed aluminum specification of 15,000 mcg/L, (b) (4) [redacted] he Applicant has agreed to manufacture a formulation with aluminum levels acceptable for all age groups by December of 2020.

The remaining excipients in CMP Developments formulation are acceptable per the toxicology review.

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 LD, support the efficacy and safety of POTASSIUM PHOSPHATES INJECTION, USP for the indications of:

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 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 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.

The risk/benefit profile of potassium phosphates is like the LD sodium phosphates, except for the difference in the salt. Potassium phosphates has 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 safety and dosing information. In conclusion, the benefits of the proposed product outweigh the potential risks, and approval of New Drug Application 212121 for POTASSIUM PHOSPHATES INJECTION, USP in adults and pediatric patients 12 years and older weighing at least 40 kg 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 (PREA) (21 U. S. C. 335), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. POTASSIUM PHOSPHATES INJECTION, USP is a new active ingredient (new salt) and therefore, triggers PREA. Currently, there is no approved and marketed formulation of potassium phosphates injection for pediatric patients of any age group. However, there is an approved NDA 018892 for SODIUM PHOSPHATES INJECTION, USP by Hospira, LLC that is indicated in all pediatric age groups. NDA 212121 relies on the FDA's findings of safety and efficacy for the listed product by Hospira. The indication for parenteral nutrition will be limited to adults and pediatric patients 12 years of age or greater weighing at least 40 kg due to the aluminum content, which is too high for younger (<12 years of age) and lighter patients (<40 kg). The maximum proposed dose in PN for pediatric patients (maximum 40 mmol/day) would provide exposure to more than 5 mcg/kg/day of aluminum for an adolescent weighing less than 40 kg, an unacceptable aluminum exposure for younger pediatric patients less than 12 years of age. In addition, the phosphorus requirement in PN for younger patients may be higher (up to 2 mmol/kg/day), resulting in a doubling of the daily aluminum exposure to 10 mcg/kg/day.

The parenteral product under NDA 212121 will also be approved as a source of phosphorus to correct hypophosphatemia in adult and pediatric patients 12 years and older. To have a consistent pediatric population definition for both indications and minimize the risk of dosing errors, this indication is also limited to adults and pediatric patients 12 years of age and older

An Agreed Initial Pediatric Study Plan (iPSP), dated December 14, 2018 under IND 122149 detailed a plan for 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 as an additive to parenteral nutrition formulas). The Applicant plans to request a deferral for the assessment in pediatric patients from neonates to less than 12 years of age, including identifying the appropriate dose regimen for this younger age group, for use in parenteral nutrition, until the time at which an age-appropriate formulation with an acceptable level of aluminum becomes available.

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 12 years of age and older (as well as younger pediatric patients down to neonates) are described in clinical practice guidelines for parenteral nutrition formulation recommendations; these guidelines generally rely upon the literature discussed in this review.

There are currently no planned pediatric pharmacokinetic (PK) studies or pediatric efficacy and safety studies. (b) (4)

Therefore, a new PREA postmarketing requirement (PMR) is proposed for the Applicant to develop an age-appropriate formulation with an acceptable aluminum content for pediatric patients less than 12 years of age and for lower-weight pediatric patients 12 years of age and older for use in parenteral nutrition. The safety risks of hyperkalemia, hyperphosphatemia, and hypocalcemia and the dosing in adolescent patients are similar to adults. The maximum dosing for use in parenteral nutrition in pediatric patients less than 12 years of age and pediatric patients weighing less than 40 kg, however, is limited by the amount of aluminum in the formulation.

Section 8.4 (Pediatric Use) will reflect that safety and effectiveness of POTASSIUM PHOSPHATES INJECTION, USP have been established in pediatric patients 12 years and older 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 parenteral nutrition indication in pediatric patients 12 years and older weighing at least 40 kg. Section 8.4 states that the safety of POTASSIUM PHOSPHATES INJECTION, USP has not been established for adolescent patients less than 40 kg or pediatric patients less than 12 years of age for parenteral nutrition. A separate Division of Pediatric and Maternal Health (DPMH) Labeling Review is in the Document Archiving, Reporting and Regulatory Tracking System (DARRTS) dated September 9, 2019.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

1. INDICATIONS AND USAGE

The LD, SODIUM PHOSPHATES INJECTION, USP, has the following indication:

> …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 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 will not be indicated for use in pediatric patients below the age of 12 years. In addition, the PN indication includes a minimum weight for both adult and pediatric patients based upon the aluminum content of the product. The safety risk posed by the aluminum content is further emphasized by inclusion of a Limitations of Use statement under the PN indication.

> **1.1. 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.
>
> **1.2 For Parenteral Nutrition**
>
> POTASSIUM PHOSPHATES INJECTION is indicated as a source of phosphorus for parenteral nutrition in adults weighing at least 45 kg and pediatric patients 12 years of age and older weighing at least 40 kg when oral or enteral nutrition is not possible, insufficient or contraindicated.
>
> Limitations of Use
> Safety has not been established for parenteral nutrition in adults weighing less than 45 kg or pediatric patients less than 12 years of age or weighing less than 40 kg due to the risk of aluminum toxicity *[see Warnings and Precautions (5.5), Use in Specific Population (8.4)].*

The FDA Established Pharmacologic Class (EPC) text phrase for labeling was proposed as "phosphorus replacement product." The official EPC (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 adverse reactions 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 12 years of age and older 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 Table 1 in the label 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 adverse reactions reported with single doses of 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 1: Recommended Initial or Single Dose of POTASSIUM PHOSPHATES INJECTION in Intravenous Fluids to Correct Hypophosphatemia in Adults and Pediatric Patients 12 Years of Age and Older

Serum Phosphorus Concentration[a]	Phosphorus Dosage[b, c]	Corresponding Potassium Content
1.8 mg/dL to 2.4 mg/dL	0.16 mmol/kg to 0.31 mmol/kg	0.25 mEq/kg to 0.49 mEq/kg of potassium
1 mg/dL to 1.7 mg/dL	0.32 mmol/kg to 0.43 mmol/kg	0.5 mEq/kg to 0.68 mEq/kg of potassium
Less than 1 mg/dL	0.44 mmol/kg to 0.64 mmol/kg[c]	0.69 mEq/kg to 1 mEq/kg of potassium

[a] Serum phosphorus reported using 2.5 mg/dL as the lower end of the reference range for healthy adults. 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 71 mEq) as a single dose.

The dosage of phosphorus in parenteral nutrition 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 shown in Table 2 in the label are general recommendations. 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 maximum daily dosage is also provided, as determined based upon the aluminum content of the product. The amount of phosphorus that can be added to parenteral nutrition may also be limited by the amount of calcium that is also added to the solution.

TABLE 2: Recommended Daily Dosage of POTASSIUM PHOSPHATES INJECTION for Parenteral Nutrition

Patient Population	Generally Recommended Phosphorus Daily Dosage (Potassium Content)	Maximum Phosphorus Dosage (Potassium Content) Based Upon Aluminum Content[a]
Adults weighing at least 45 kg	20 mmol/day to 40 mmol/day[b] (potassium 31 mEq/day to 62.7 mEq/day)	45 mmol/day (potassium 71 mEq/day)
Pediatric patients 12 years of age and older weighing at least 40 kg		40 mmol/day (potassium 62.7 mEq/day)

[a] *see Warnings and Precautions (5.5), Use in Specific Populations (8.4)*
[b] 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.

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.

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 electrocardiographic (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.

Route and Intravenous Infusion Rate

- The concentration of the diluted solution and the infusion rate is dependent upon whether administration will be through a peripheral or central venous catheter.

  Peripheral administration:
  - The maximum recommended concentration is phosphorus 6.4 mmol/100 mL (potassium 10 mEq/100 mL).
  - The maximum recommended infusion rate is approximately phosphorus 6.4 mmol/hour (potassium 10 mEq/hour)

  Central administration:
  - The maximum recommended concentration is phosphorus 18 mmol/100 mL (potassium 28.2 mEq/100 mL).
  - The maximum recommended infusion rate is approximately phosphorus 15 mmol/hour (potassium 23.5 mEq/hour).

- Continuous electrocardiographic (ECG) monitoring and infusion through a central venous catheter, is recommended for infusion rates of potassium higher than 10 mEq/hour in adults and 0.5 mEq/kg/hour in pediatric patients 12 years of age and older.

Monitoring

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

4. CONTRAINDICATIONS

The product is contraindicated in patients with various laboratory abnormalities: hyperkalemia (exacerbated by potassium component of the product), hyperphosphatemia, hypercalcemia (risk of calcium-phosphate precipitates) and significant hypocalcemia (worsening of existing

hypocalcemia); and in patients with severe renal impairment and end stage renal disease, due to the risks of excess phosphorus and/or potassium.

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 - Serious Cardiac Adverse Reactions with Undiluted, or Bolus or Rapid Intravenous Administration of the review).

5.2. Pulmonary Embolism Due to Pulmonary Vascular Precipitates

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

5.3. Hyperkalemia

This section describes the adverse reactions associated with the potassium component of the product and patients at risk (severe renal impairment and end stage renal disease, 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 adapted from the CFR 201.323e is included along with the specific risk from this product (see Section 5.2.1 of the review).

> Exposure to aluminum from POTASSIUM PHOSPHATES INJECTION is not more than 4.9 mcg/kg/day when:
>
> - adults weighing at least 45 kg are administered the recommended maximum dosage of phosphorus (45 mmol/day) for parenteral nutrition.
> - pediatric patients 12 years of age and older weighing at least 40 kg are administered the recommended maximum dosage of phosphorus (40 mmol/day) for parenteral nutrition *[see Dosage and Administrations (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 aluminium from the admixture should be considered and maintained at no more than 5 mcg/kg/day *[see Use in Specific Populations (8.4)].*

(b) (4)

[redacted]

5.6. Hypomagnesemia

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

5.7. Vein Damage and Thrombosis

Class labeling for parenteral nutrition 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 and as reported in postmarketing are included. See Section 8.2.4 and 8.2.7 of this review.

7. DRUG INTERACTIONS

The risk of hyperkalemia when the product is coadministered 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 8.2.7 of this review.

8.4 Pediatric Use

The indicated populations and the risks associated with aluminum toxicity are described. See Section 10 - Pediatrics 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 8.2.7 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 (REMS)

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 Commitment

The following will be issued:

1) **CMC PMC 3714-1:**

   Submit the assay results of the PN admixture studies as proposed in the PN Admixture Compatibility Stability Protocol.

   Final Report Submission: 10/19

   Reasoning for requesting study
   The Applicant conducted a compatibility study (Protocol 0009) to demonstrate the safety and efficacy of admixing the drug product with parenteral nutrition (PN). The Applicant provided the results for visual description, pH and particulate matters 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 PDUFA goal date, the actual assay results to confirm its strength so that the safety and efficacy are not compromised, due to delayed HPLC method development. However, the Applicant has committed to submit this data post-approval by October 30th 2019. Since it is very unlikely that the assay results will be significantly changed when no precipitation has been observed, it is deemed acceptable for the applicant to submit the assay results for the PN admixture studies post approval.

2) **PREA PMR 3714-2**:

   Develop an age-appropriate formulation for POTASSIUM PHOSPHATES INJECTION, USP with acceptable aluminum content and weight-based dosing criteria to ensure accurate dosing for pediatric patients less than 12 years of age.

   Final Report Submission: 12/20

   Reasoning for requesting study
   To address the risk of aluminum toxicity with the current formulation for patients younger than 12 years of age, an age-appropriate formulation with

lower aluminum content is needed, (b) (4) [redacted]. When the data are available for the age-appropriate formulation, CMP Development, LLC will update the appropriate sections of Module 3 for the new strength and include at least 3 months of stability information at the time of submission. Note, should the age-appropriate formulation differ significantly from the current POTASSIUM PHOSPHATES INJECTION, USP (e.g., different excipients), then additional information may be required.

This will be the first approved potassium phosphate product on the market. There are only unapproved marketed potassium products. Both potassium phosphates injection and SODIUM PHOSPHATES INJECTION, USP are frequently in shortage. The currently proposed formulation has acceptable aluminum levels for pediatric patients age 12 and older, weighing at least 40 kg and adults weighing at least 45 kg, and can be approved for these populations at this time.

The Applicant conducted a compatibility study to demonstrate the safety and efficacy of admixing the drug product with parenteral nutrition (PN). The Applicant provided the results for visual description, pH and particulate matters 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 PDUFA goal date, the actual assay results to confirm its strength so that the safety and efficacy are not compromised, due to delayed HPLC method development. However, the Applicant has committed to submit this data by October 30th, 2019, post-approval. Since it is very unlikely that the assay results will be significantly changed when no precipitation has been observed, it is deemed acceptable for the applicant to submit the assay results for the PN admixture studies post approval.

14. Division Director Comments

The proposed indications for POTASSIUM PHOSPHATES Injection are very similar to those of the LD, SODIUM PHOSPHATES INJECTION, USP (NDA 018892). The major differences are that the current product is not indicated for use by pediatric patients below the age of 12 years, and that the PN indication specifies a minimum weight for both adult and pediatric patients. For the PN indication, these differences in the indicated population are warranted based upon the aluminum content of the current formulation. Use of the product in PN by younger pediatric patients, or patients below the specified weights, would expose the patients to levels of aluminum that are unacceptable based on CFR 201.323, given that PN dosing is not weight-based. This difference in the indicated population from the LD is emphasized by inclusion of a Limitations of Use statement under the PN indication.

For the correction of hypophosphatemia indication, although the CFR does not mandate an acceptable aluminum exposure level for non-PN intravenous infusions, the Applicant has also proposed to limit the pediatric population to patients aged 12 years and above. This is acceptable because maintaining a consistent pediatric target population for both indications may help minimize prescribing errors.

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 aged 12 years and above, the review team considered published literature that included clinical efficacy studies for both indications in adults. These studies were typically open-label studies that relied upon changes in serum phosphorus levels with IV 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. Dosing for pediatric patients 12 years and older was derived from adult data that identified a dosing algorithm that resulted in correction of hypophosphatemia, given the similar phosphorus requirements and understanding of the physiology of phosphorus repletion over both adults and pediatric patients 12 years and older.

Dosing for the 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 “[s]erum sodium, phosphorus and calcium levels should be monitored as a guide to dosage,” but no specific dosage is mentioned for any age groups. Therefore, the dosing recommendations for adults for this indication for POTASSIUM PHOSPHATES INJECTION 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. Based upon clinical requirements, some patients may require a higher or lower dose. For pediatric patients 12 years and older, 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 12 years and older.

The maximum recommended initial or single dose for correction of hypophosphatemia is phosphorus 45 mmol, due to the risk of serious cardiac adverse reactions reported with undiluted, bolus or rapid IV administration (i.e., 50 mmol and above and/or administered over 1-3 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 vs. 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 post-marketing safety reports.

Dosing for the 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 of 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, the dosing recommendation for adults and pediatric patients 12 years and older is 20-40 mmol/day added to PN, based on published literature in adults. 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 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.

Due to likely longer-term use of POTASSIUM PHOSPHATES Injection in PN, and regulations that limit the exposure to aluminum in PN products, the dosage was limited by the aluminum content of this product. The Division proposes to set limits on maximum daily dose that are specific for the indicated populations identified by age group and minimum weight. The maximum daily phosphorus dose for adults weighing at least 45 kg is capped at 45 mmol, and for pediatric patients aged 12 years and older and weighing at least 40 kg, the daily dose is capped at 40 mmol. 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. Of note, given higher recommended PN dosage for infants in the LD's labeling, and higher phosphate requirements in younger pediatric patients generally, this product as currently formulated would provide an unacceptably high level of aluminum exposure if administered to pediatric patients below the age of 12 years.

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 adverse events 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. 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 prior to administration and maximum infusion rates for peripheral and central venous administration will be prominently labeled.

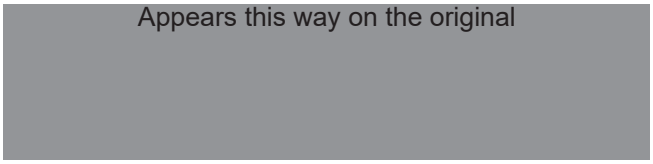
PMR/PMC:

As noted, the aluminum content of the current formulation has precluded inclusion of pediatric patients of all ages in the indicated population. The pediatric assessment in patients younger than 12 years has been deferred, and the Applicant has agreed to a PREA PMR to develop an age-appropriate formulation with an acceptable aluminum content and weight-based dosing criteria to ensure accurate dosing for pediatric patients less than 12 years of age. This will be submitted by December 2020.

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, but the Sponsor committed to provide these results by October 31, 2019. 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 post-marketing commitment, and that the lack of these assay results do not constituent a bar to approval.

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. Limitations in the target population for the two indications are warranted based on the aluminum content of the proposed product, along with the benefit of maintaining a consistently defined pediatric age group across both indications. While complete dosing recommendations were absent in the LD, there was no suggestion that differential dosing was needed for adults and pediatric patients aged 12 years and older. The review team relied upon the published adult literature, as well as on safety considerations relating to aluminum exposure to develop dosing recommendations for both indications. I concur with the recommendation from the review team that this product be approved.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15. Appendices

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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 prescribing information (PI), container label and carton labeling identified areas of vulnerability that may lead to medication errors. PI recommendations, as well as, container label and carton labeling recommendations communicated to the Sponsor have been provided in our July 15, 2019, September 3, 2019 and September 6, 2019 label and labeling reviews (Abraham 2019a; Abraham 2019b; Abraham 2019c).

On June 19, 2019, we searched FAERS using the criteria in the table below and identified 108 case reports. We individually reviewed the cases, and limited our analysis to cases that described medication errors associated with potassium phosphate injection or sodium phosphate injection. We used the NCC MERP Taxonomy of Medication Errors to code the type of error and factors contributing to the errors when enough information was provided by the reporter (The National Coordinating Council for Medication Error Reporting and Prevention 2001). We excluded 88 reports that were associated with oral or rectal dosage forms (e.g., Visicol, Neutra-Phos, sodium phosphate enema), 1 report involving sodium chloride and sodium acetate (not potassium phosphate or sodium phosphate), and 1 report that described the use of a potassium phosphate product, a week prior to receiving a recall notice for the product.

Of the remaining eighteen relevant cases most of the cases (n=17/18) were associated with potassium phosphate and involved wrong drug errors (n=8/18) followed by preparation errors (n=5/18), wrong dose errors (n=4/18), and wrong dose and wrong drug error (n=1/18). Eleven patients were impacted by the error, including ten cases that reported a serious outcome (death: 7, and “arrested”, “cardiac arrest” or “required resuscitation”: 3). The ten cases describing a serious outcome were associated with preparation errors (e.g., not diluted or incorrectly diluted prior to administration, wrong concentration compounded), wrong dose error secondary to miscalculation or transcribing a verbal order, and wrong drug error (e.g., solution compounded with calcium gluconate instead of the intended potassium phosphate).

As currently presented, the dilution warning in the prescribing information (PI) is expressed as a negative statement, “Not for direct injection.” Although no root cause could be attributed to the medication error cases reviewed, post-marketing reports have shown negative statements may have the opposite of the intended meaning because the word ‘not’ may be overlooked and the warning may be misinterpreted as an affirmative action. In order to potentially further mitigate the risk for medication preparation and administration errors, we provided alternative language for the PI to the Division in our July 15, 2019 review.

Moreover, we note that the proposed container label and carton labeling prominently stated the “Must be Diluted” statement, however to ensure proper administration of drug product, we provided additional recommendations for the container label and carton labeling to the Applicant in our reviews.

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

/s/

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09/19/2019 04:05:45 PM

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