CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212121Orig1s000

PRODUCT QUALITY REVIEW(S)

Memorandum

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

Date: **September 17, 2019**
From: **Hitesh Shroff, Ph.D.**
Application Technical Lead, Branch V
Division of New Drug Products II
Office of New Drug Products

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

To: **CMC Review #1 of NDA 212121**

Subject: Final Recommendation for NDA 212121

At the time when the CMC Review #1 was completed on August 27, 2019 it had noted the following pending issues:

The label/labeling issues have not been completely resolved.

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

The applicant submitted the revised the Prescribing Information (PI) on September 13, 2019 and immediate container on September 6, 2019. The resubmitted CMC sections of the labeling/labels acceptable. **(See the Attachment 1)**

In the amendment submitted on September 17, 2019 the applicant agreed to the following Post-Marketing Commitment to provide the TPN admix assay data from the study described in Protocol 0009 (submitted in amendment 0009 dated 6/25/2019) by October 30, 2019.

- 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 to 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 (post approval) the assay results for the TPN admixture studies (Protocol 0009 submitted in amendment 0009 dated 6/25/2019). **(see Attachment 2)**

Recommendation:

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

Application Technical Lead's Assessment and Signature

The NDA is recommended for Approval from quality perspective.

Hitesh Shroff, Ph.D.
Application Technical Lead,
Branch V Division of New Drug Products II
September 17, 2019

Hitesh N. Shroff -S

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Attachment 1

I. PI

Highlights of Prescribing Information Section

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use POTASSIUM PHOSPHATES INJECTION safely and effectively. See full prescribing information for POTASSIUM PHOSPHATES INJECTION.

POTASSIUM PHOSPHATES INJECTION, for intravenous use
Initial U.S. Approval: 1983

----------INDICATIONS AND USAGE ----------

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. (1.1)
- 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. (1.2)

----------DOSAGE AND ADMINISTRATION----------

- Administer intravenously only after dilution and admixing in a larger volume of fluid. (2.1)
- POTASSIUM PHOSPHATES Injection provides phosphorus 3 mmol/mL (potassium 4.7 mEq/mL). (2.2, 2.4)
- Monitor serum phosphorus, potassium, calcium, and magnesium concentrations. (2.2, 2.4)
- See full prescribing information for instructions on preparation and administration. (2.1, 2.3)

Recommended Dosage for Correction of Hypophosphatemia in Intravenous Fluids:

- POTASSIUM PHOSPHATES Injection is only for administration to a patient with a serum potassium concentration less than 4 mEq/dL; otherwise, use an alternative source of phosphate. (2.1)
- The dosage and rate of administration are dependent upon the individual needs of the patient, and the contribution of phosphorus and potassium from other sources. (2.2)
- See full prescribing information for recommendations on single dosing, repeated dosing and infusion rate. (2.1, 2.2)

Recommended Dosage for Administration in Parenteral Nutrition:

- Individualize the dosage based upon the patient's clinical condition, nutritional requirements, and the contribution of oral or enteral phosphorus and potassium intake. (2.4)
- See full prescribing information for recommendations for daily and maximum dosage. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: phosphorus 45 mmol/15 mL (3 mmol/mL) and potassium 71 mEq/15 mL (4.7 mEq/mL) in a single-dose vial. (3)

----------CONTRAINDICATIONS----------

- hyperkalemia
- hyperphosphatemia (4)
- hypercalcemia or significant hypocalcemia (4)
- severe renal impairment (eGFR less than 30 mL/min/1.73m^2) and end stage renal disease (4)

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

- Serious Cardiac Adverse Reactions with Undiluted, Bolus, or Rapid Intravenous Administration: Administer only after dilution and admixing; do not exceed the recommended infusion rate. Continuous electrocardiographic (ECG) monitoring may be needed during infusion. (5.1)
- Pulmonary Embolism due to Pulmonary Vascular Precipitates: If signs of pulmonary distress occur, stop the infusion and initiate a medical evaluation. (5.2)
- Hyperkalemia: Increased risk in patients with renal impairment, severe adrenal insufficiency, or treated with drugs that increase potassium. Patients with cardiac disease may be more susceptible. Do not exceed the maximum daily amount of potassium or the recommended infusion rate. Continuous ECG monitoring may be needed during infusion. (5.3, 7.1)
- Hyperphosphatemia and Hypocalcemia: Monitor serum phosphorus and calcium concentrations during and following infusion. (5.4)
- Aluminum Toxicity: Increased risk in patients with renal impairment, including preterm infants. (5.5, 8.4).
- Hypomagnesemia: Reported in patients with hypercalcemia, diabetic ketoacidosis and renal tubular acidosis. Monitor serum magnesium concentrations during treatment. (5.6)
- Vein Damage and Thrombosis: Infuse concentrated or hypertonic solutions through a central catheter. (2.1, 2.3, 5.7)

----------ADVERSE REACTIONS----------

Adverse reactions are hyperkalemia, hyperphosphatemia, hypocalcemia and hypomagnesemia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact CMP Pharma at 1-844-321-1443 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Use of Other Medications that Increase Potassium: Avoid use in patients receiving such products. If use cannot be avoided, closely monitor serum potassium concentrations. (5.3, 7.1)

----------USE IN SPECIFIC POPULATIOS----------

Pediatrics: Safety has not been established in pediatric patiens less than 12 years of age or in adolescents weighing less than 40 kg due to the risk of aluminum toxicity. (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised:09/2019

Section 3 Dosage Forms and Strengths

3 DOSAGE FORMS AND STRENGTHS

Potassium Phosphates Injection, USP: phosphorus 45 mmol/15 mL (3 mmol/mL) and potassium 71 mEq/15 mL (4.7 mEq/mL) as a clear and colorless solution in a single-dose vial.

Section 11 Description

11 DESCRIPTION

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.

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

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

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

Each mL contains 175 mg of monobasic potassium phosphate and 300 mg of dibasic potassium phosphate.

Each mL contains 3 mmol phosphorus (equivalent to 93 mg phosphorous) and 4.7 mEq potassium (equivalent to 184 mg of potassium). Note: 1 mmol of phosphorus is equal to 1 mmol phosphate. The pH is 6.5 to 7.5.

This product contains no more than 15,000 mcg/L of aluminum *[see Warnings and Precautions (5.5)]*.

The osmolar concentration is 7.7 mOsmol/mL (calc).

Section 16 How Supplied/Storage and Handling

16 HOW SUPPLIED/STORAGE AND HANDLING

POTASSIUM PHOSPHATES Injection, USP: phosphorus 45 mmol/15 mL (3 mmol/mL) and potassium 71 mEq/15 mL (4.7 mEq/mL) as a clear and colorless solution supplied in a 15 mL single-dose glass vial (NDC 46287-024-15) in a single count carton (NDC 46287-024-15).

Store at 2°to 8°C (36°to 46°F). Do not freeze.

For storage of admixed solution *see Dosage and Administration 2.2, 2.4.*

II. Labels

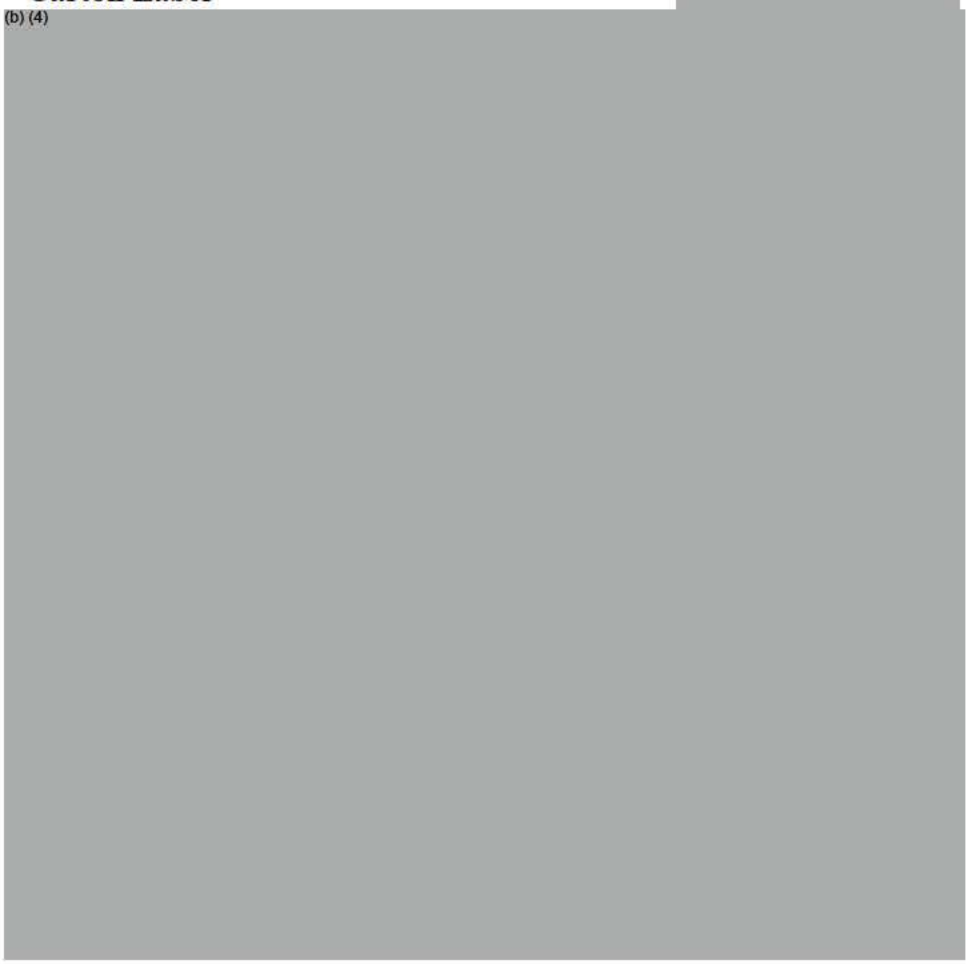
Immediate Container Label

(b) (4)

Carton Label

(b) (4)

(b) (4)



Attachment 2

CMC PMC Development Template

For non-506B reportable chemistry, manufacturing, and controls (CMC)
Post-marketing commitments (PMC) only

DARRTS Function Code: FRM-PMRPMC-03

- This template should be completed by the Office of Pharmaceutical Quality (OPQ) reviewer and signed in DARRTS by the applicable OPQ Signatory.
- Multiple CMC PMCs for the same application may be included on a single Development Template. Copy sections 1-3 for each PMC.
- Do not use this form for post-marketing requirements (PMRs) or 506B reportable PMCs.

NDA/BLA #: 212121
Product Name: Potassium Phosphates Injection

1. PMC Information

PMC and # (XXXX-X)	3714
PMC Description:	Submit the assay results of the TPN admixture studies as proposed in the TPN Admixture Compatibility Stability Protocol
Final Report Submission	October 30, 2019
Explain the review issue and the goal of the study	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 to 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 (post approval) the assay results for the TPN admixture studies (Protocol 0009 submitted in amendment 0009 dated 6/25/2019).
What type of study is agreed upon?	☐ Quality CMC study (e.g., assay, dissolution testing, drug substance characterization, intermediates characterization, impurity characterization, manufacturing process issues, potency, product delivery, reformulation, sterility) ☒ Quality stability study

2. Check why this issue is appropriate for the PMCs listed above instead of requiring it pre-approval.

- [x] Unmet need for drug or life-threatening condition
- [ ] Long-term data needed (e.g., stability data)
- [x] Only feasible to conduct post-approval
- [ ] Improvements to methods
- [ ] Theoretical concern
- [ ] Manufacturing process analysis
- [ ] Other (describe in text box below)

See also the explanation above in the box titled "Explain the review issue and the goal of the study". The result of this assay study is not likely to affect the determination of safety of use of potassium phosphates injection in PN

3. To be completed by the Signatory for PMCs (check with RBPM for applicable signatory depending on OPQ Offices):

- [x] Does the study meet criteria for PMCs?
- [ ] Are the objectives clear from the description of the PMC?
- [ ] Has the applicant adequately justified the choice of schedule milestone dates?
- [ ] Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

As explained above, the risk involved in the PMC is deemed extremely low, and therefore, the way as proposed for PMC is acceptable.

Signatory: __Moo-Jhong Rhee, Ph.D.
Branch Chief, ONDP/OPQ_____

- [ ] This *PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality. (Your electronic signature will be appended when this document is entered into the archival system.)*

QUALITY ASSESSMENT

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

NDA 212121

OPQ Review #1

Drug Name/Dosage Form	Potassium Phosphates Injection, for intravenous use
Strength	45 mmol phosphorus/15 mL (3 mmol phosphorus/mL) in a single-dose vial. Also contains: 71 mEq potassium /15 mL (4.7 mEq potassium/mL)
Route of Administration	Injection
Rx/OTC Dispensed	Rx
Applicant	CMP Development LLC, Farmville, NC
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	March 19, 2019	OPQ
Amendment	May 24, 2019	OPF, ONDP, DMA
Amendment	June 11, 2019	ONDP, DMA
Amendment	June 25, 2019	ONDP
Amendment	July 22, 2019	ONDP
Amendment	July 29, 2019	ONDP, DMA
Amendment	August 1, 2019	ONDP
Amendment	August 19, 2019	ONDP
Amendment, Labeling	August 21, 22019	ONDP

Quality Review Team

DISCIPLINE	REVIEWER	Secondary Assessment
Drug Substance	Jeffrey B. Medwid	Donna Christner
Drug Product and Labeling	Zhengfang Ge	Moo-Jhong Rhee
Process	Sydney Choi	Yaodong Huang
Microbiology	Laura Wasil	Erika Pfeiler
Facilities	Sydney Choi	Yaodong Huang
Regulatory Business Process Manager	Oumou Barry	N/A
Application Technical Lead	Hitesh Shroff	N/A
Environmental Analysis (EA)	Zhengfang Ge	Moo-Jhong Rhee

QUALITY ASSESSMENT

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	Potassium Phosphate *Monobasic*	Active	Reviewed by Dr. Srinivasa Murphy on January 14, 2017	LOA: June 13, 2017
	Type II		Potassium Phosphate *Dibasic*	Active	Reviewed by Dr. Jeffrey B. Medwid on July 17, 2019	LOA: June 13, 2017
	Type III	(b) (4)	Glass vials	Active	Not reviewed, Information provided in NDA	LOA July 11, 2017
	Type III	(b) (4)	(b) (4) stopper	Active	Not reviewed, Information provided in NDA	LOA June 28, 2017
	Type III		(b) (4) stopper	Active	Reviewed by Dr. Laura R. Wasil on March 4, 2019	LOA June 28, 2017
	Type V	(b) (4)	(b) (4)	Active	Reviewed by Dr. Laura R. Wasil on April 24, 2019	LOA November 7, 2018

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	122149	From the same applicant and for the same indication
NDA	018892	Sodium phosphates injection from Hospira as RLD for reliance on the FDA's previous findings of safety and efficacy.

2. CONSULTS: None

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

Executive Summary

I. Recommendations and Conclusion on Approvability

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed Potassium Phosphates injection, 45 mmol Phosphorus/15 mL (3 mmol Phosphorus/mL) containing 47 mmol Potassium/15 mL (4.7 mEq Potassium/mL)

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

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

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

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

II. Summary of Quality Assessments

A. Product Overview

Potassium Phosphates injection, 45 mmol Phosphorus/15 mL (3 mmol Phosphorus/mL) containing 47 mmol Potassium/15 mL (4.7 mEq Potassium/mL) is a sterile, nonpyrogenic, concentrated solution containing monobasic potassium phosphate and dibasic potassium phosphate in Water for Injection, USP, as an additive to intravenous solutions for parenteral nutrition. There are no preservatives or anti-oxidants in this formulation.

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

Proposed Indication(s) including Intended Patient Population	Potassium Phosphates Injection is a phosphorus replacement product indicated in adults and pediatric patients 12 years of age and older as: • to prevent or correct hypophosphatemia in patients with restricted or no oral intake. • for parenteral nutrition when oral or enteral nutrition is not possible, insufficient or contraindicated.
Duration of Treatment	As needed
Maximum Daily Dose	Recommended Dosage: • Potassium Phosphates Injection provides 3 mmol/mL of phosphorus. • The dosage and rate of administration are dependent upon the individual needs of the patient. Monitor serum phosphorus, potassium and calcium and adjust the dosage accordingly. (b) (4)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substances:

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

Potassium phosphate monobasic 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.

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

The overall quality of potassium phosphate monobasic is controlled by its specification, which includes description, identification tests per USP <191> for potassium and phosphates; (b) (4) [redacted] The particle size and polymorphs of potassium phosphate monobasic are not important because the drug product is a solution as injection.

The applicant has provided batch analyses of four batches of potassium phosphate monobasic used in the drug product manufacturing. A re-test period of (b) (4) [redacted] months is proposed and acceptable. The DMF (b) (4) [redacted] was reviewed by Dr. Jeffrey B. Medwid and was deemed adequate from the CMC perspective. (See **the Drug Substance** review)

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

Potassium phosphate dibasic is a white to off-white odorless powder. It is very soluble in water. Its melting point is >465°C (decompose) and crystal density is 2.44 g/cc. Its molecular formula is K_2HPO_4 and its molecular weight is 174.20.

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

The overall quality of potassium phosphate dibasic is controlled by its specification, which includes description, identification tests per USP <191> for potassium and phosphates; (b) (4) [redacted] The particle size and polymorphs of potassium phosphate dibasic are not important because the drug product is a solution as injection.

The applicant has provided batch analyses of five batches of potassium phosphate dibasic used in the drug product manufacturing. A re-test period of (b) (4) months is proposed and acceptable. The DMF (b) (4) was reviewed by Dr. Jeffrey B. Medwid and was deemed adequate from the CMC perspective. (See **the Drug Substance** review)

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

Drug Product:
Potassium Phosphate Injection, USP, 45 mmol phosphorus/15 mL (3 mmol phosphorus/mL) is a sterile, nonpyrogenic, aqueous solution of potassium phosphate monobasic and potassium phosphate dibasic. The drug product is diluted or added to TPN solution prior to intravenous administration. The drug product contains 175 mg/mL of potassium phosphate monobasic and 300 mg/mL of potassium phosphate dibasic in Water for Injection. There are no preservatives or anti-oxidants in the drug product formulation so unused portion should be discarded.

The drug product is supplied as a 15 mL clear USP Type 1 glass vial, closed with a (b) (4) stopper and sealed with a (b) (4) cap.

The drug product specification includes description and confirmation of potassium and phosphate per USP <191> as identity tests, (b) (4) particulate matter per USP <788> and (b) (4)

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

The potassium phosphate injection admixture compatibility study was conducted with normal saline solution, 5% dextrose in water (D5W), Clinimix-E and Kabiven. For this study, appearance, pH and particulate matter were assessed. No precipitates of phosphate salts were observed in the admixed solutions. Thus, the drug product appears to be compatible with these diluents and TPN solutions.

Based on the satisfactory 12-month long-term stability in upright and inverted positions at 5°C and 6-month accelerated stability data at 25°C from three primary registration batches of the drug product, the proposed **24-month of expiration dating period** is granted when stored at 5°C in the proposed container closure system per drug product reviewer, Dr. Zhengfang Ge (see the **Drug Product** review).

Manufacturing:
The drug product is manufactured by (b) (4)
The key drug product manufacturing process includes: (b) (4)

(b) (4)

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

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

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

Environmental Assessment: The applicant requested categorical exclusion for environmental analysis [21 CFR 314.50 (d)(1) 9iii)] on the basis that this product will not be administered at higher dosage levels, for longer duration, or for different indications than were previously in effect. To the applicant's knowledge, no extraordinary circumstances exist. In addition, the applicant certified that the production of this product meets the requirements of all Federal, State and Local Environmental Laws. Therefore, claim of a categorical exclusion from the requirements of an environmental assessment (EA) in accordance with 21 CFR Part 25.31(a) was deemed acceptable. (See the **Drug Product** review)

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

C. Post Approval Commitment:
Post- marketing Commitment to submitting assay results of TPN admixture studies **by Oct 31, 2019**

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

G. List of Deficiencies:

The following deficiencies should be resolved with the applicant:

For Container/Carton Labels

1. Correct the names of active ingredients from "monobasic potassium phosphate (b) (4) and "dibasic potassium phosphate (b) (4) " to read "Each mL contains monobasic potassium phosphate 175 mg, dibasic potassium phosphate 300 mg"

2. Revise the content of aluminum from "Contains no more than 1500mcg/L" to an acceptable limit per Agency recommendation.

3. Add "Do not freeze" Add "Do not freeze"

Application Technical Lead Name and Date:

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
August 27, 2019

Hitesh N. Shroff -S
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Assessment: ***Adequate***

R REGIONAL INFORMATION

Environmental Assessment

The applicant provided an environment assessment per 21 CFR 314.50 (d) (l) (iii), which states that the applicant requires a claim for Categorical Exclusion per 21 CFR 25.31 (c) because the drug product will not be administered at higher dosage levels, for longer duration, or for different indications than were previously in effect. The applicant claimed a Categorical Exclusion per 25.31 (c), and stated that, to the applicant's knowledge, no extraordinary circumstances exist.

In addition, the applicant certifies that the production of this product meets the requirements of all Federal, State and Local Environmental Laws.

Assessment: ***Adequate***

Methods Validation or Verification Package

Assessment: ***Adequate***

See review for Analytical Methods in section P.5

Comparability Protocols

Assessment: ***{Adequate/Inadequate}***
N/A

Post-Approval Commitments

Assessment: ***Adequate***
Postmarketing Commitment to submitting assay results of TPN admixture studies **by Oct 31, 2019**

Lifecycle Management Considerations

N/A

DRUG PRODUCT LIST OF DEFICIENCIES

None

Primary Drug Product Assessor Name and Date:

Zhengfang Ge, Ph. D.
Reviewer, BRANCH V/DIVISION II
OFFICE OF NEW DRUG PRODUCT

Secondary Assessor Name and Date (and Secondary Summary, as needed):
The proposed drug product, Potassium Phosphates Injection, 3 mM P/mL is a small volume parenteral product (SVP) intended to supply source of phosphates to patients via intravenous administration. During the review, two issues were surfaced: 1) since this product is to be admixed with other LVPs as TPN therapies, the admixture should not introduce any significant impact on the integrity of the drug product as well as LVPs before it is introduced to the patients; 2) the presence of aluminum in the drug product should be assured to be within the regulatory limits to protect the patients from the aluminum toxicity.

I agree with Dr. Ge's assessment on the overall control strategy for the quality of the proposed drug product including issues mentioned above, and therefore, I concur with her recommendation of **approval** of this application from the drug product perspective.

Moo-Jhong Rhee, Ph. D.
Branch Chief, BRANCH V/DIVISION II
OFFICE OF NEW DRUG PRODUCT

Zhengfang Ge

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Moo Jhong Rhee

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

The Prescribing Information is deemed not ADEQUATE as proposed until it is revised satisfactorily to meet the regulatory requirements (See the **List of Deficiencies** at the end of this review).

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	not proposed	

Established name(s)	potassium phosphates injection	Adequate Per USP monograph title
Route(s) of administration	injection	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Injection: 45 mmol phosphorus/15 mL (3 mmol phosphorus/mL) in a single-dose vial. Also contains: 71 mEq potassium /15 mL (4.7 mEq potassium/mL)	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Single dose glass vial	Adequate

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Provided in section 2.1-2.3 as shown above including the information for preparation and storage of admixture	Adequate The applicant provided admixture compatibility study that support the drug product to be admixed with NS, D5W and TPN

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Potassium Phosphates Injection, USP, 45 mmol phosphorus/15 mL (3 mmol phosphorus/mL): clear and colorless solution in a single-dose vial. Also contains 71 mEq potassium /15 mL (4.7 mEq potassium/mL).

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Injection	Adequate
Strength(s) in metric system	45 mmol phosphorus/15 mL (3 mmol phosphorus/mL)	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	Adequate The equivalency statements made in the Description section are adequate, and no need to include here per the Labeling Tool
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Clear colorless solution	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"		
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Single dose	Adequate

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	POTASSIUM PHOSPHATES	Adequate
Dosage form(s) and route(s) of administration	Injection	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Each mL contains 175 mg of monobasic potassium phosphate and 300 mg of dibasic potassium phosphate 1 mmol Phosphorus equal to 1 mmol phosphate	Adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Water for injection	Adequate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Water for injection	Adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	... is a sterile, nonpyrogenic, concentrated solution	Adequate
Pharmacological/ therapeutic class	phosphorus replacement product	Adequate
Chemical name, structural formula, molecular weight	Monobasic Potassium Phosphate is chemically designated KH_2PO_4, molecular weight 136.09, white, odorless crystals or granules freely soluble in water. Dibasic Potassium Phosphate is chemically designated K_2HPO_4, molecular weight 174.18, colorless or white granular salt freely soluble in water.	Adequate

If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	The pH is 6.5 to 7.5. This product contains no more than 15,000 mcg/L of aluminum *[see Warnings and Precautions (5.6)]*. The osmolar concentration is 7.7 mOsmol/mL (calc).	**Not Adequate** Aluminum limit needs to be revised per Pharm/tox's recommendation

Section 11 (DESCRIPTION) Continued

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

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Injection	Adequate
Strength(s) in metric system	45 mmol phosphorus/15 mL (3 mmol phosphorus/mL). Also contains 71 mEq potassium /15 mL (4.7 mEq potassium/mL).	Adequate
Available units (e.g., bottles of 100 tablets)	Supplied in a 15 mL single-dose glass vial in a single count carton	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	clear and colorless solution	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"		
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Supplied in a 15 mL single-dose glass vial in a single count carton	Adequate
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Do not freeze. For storage of admixed solution *see Dosage and Administration 2.3.*	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 2°to 8°C (36°to 46°F). Do not freeze.	Adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made	N/A	

with natural rubber latex. Avoid statements such as "latex-free."		
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling

N/A

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Distributed by: CMP Pharma Inc. 8026 US Highway 264A, Farmville, NC 27828	Adequate

2.0 PATIENT LABELING

N/A

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)

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

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Potassium Phosphates Injection, USP	Adequate
Dosage strength	45 mmol Phosphorus /15 mL (3mmol Phosphorus/mL) Also contains: 71 mEq Potassium/15 mL (4.7mEq Potassium /mL)	Adequate
Route of administration	Injection For intravenous infusion after dilution and admixing only	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Each mL contains monobasic phosphate (b) (4) 175 mg, potassium phosphate dibasic (b) (4) 300 mg	**Not Adequate** The equivalency statement is deemed adequate. However, the names of active ingredients need to be corrected to "Each mL contains monobasic potassium phosphate 175 mg, dibasic potassium phosphate 300 mg"
Net contents (e.g. tablet count)	15 mL single dose	Adequate
"Rx only" displayed on the principal display	Provided	Adequate
NDC number	Provided	Adequate
Lot number and expiration date	Provided	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 2°-8°C (36°-46°F)	**Not Adequate** Add "Do not freeze"
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	15 mL Single dose vial	Adequate
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	Caution: Must be diluted	Adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Provided	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	DISTRIBUTED BY: PHARMA Farmville, NC 27828	Adequate
Medication Guide (if applicable)	N/A	
No text on Ferrule and Cap overseal	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available	(b) (4)	**Not Adequate** • Correct the names of active ingredients from "monobasic potassium phosphate (b) (4) " and "potassium phosphate dibasic (b) (4) " to read "monobasic potassium phosphate" and "dibasic potassium phosphate" • Revise the content of aluminum to "Contains no more than XXXX mcg/L" • Add "Do not freeze"

Assessment of Carton and Container Labeling: *Inadequate*

See the deficiencies delineated below:

ITEMS FOR ADDITIONAL ASSESSMENT

The following deficiencies should be conveyed to the applicant:

For Container/Carton Labels

1. Correct the names of active ingredients from "monobasic potassium phosphate (b) (4) " and "potassium phosphate dibasic (b) (4) " to read "monobasic potassium phosphate" and "dibasic potassium phosphate"
2. Revise the content of aluminum from "Contains no more than 15,000mcg/L" to an acceptable limit per Agency recommendation.
3. Add "Do not freeze"

Overall Assessment and Recommendation:

The NDA is not ready for approval in its present form until the outstanding labeling issues listed above are satisfactorily resolved.

Primary Labeling Assessor Name and Date:

Zhengfang Ge, Ph. D.
Reviewer, BRANCH V/DIVISION II
OFFICE OF NEW DRUG PRODUCT

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

I agree with Dr. Ge's assessment on the labeling/labels and concur with her recommendation that this application not ready for approval in its present form per 21 CFR314.125(b)(6).

Moo-Jhong Rhee, Ph. D.
Branch Chief, BRANCH V/DIVISION II
OFFICE OF NEW DRUG PRODUCT

Zhengfang Ge

Digitally signed by Zhengfang Ge
Date: 8/23/2019 04:24:06PM
GUID: 508da7210002a030e76df4f60ccd142a

Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 8/23/2019 04:45:06PM
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CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	212121
Assessment Cycle Number	MR01
Drug Product Name/ Strength	Potassium Phosphates Injection USP/ 3 mM P/mL
Route of Administration	Intravenous injection
Applicant Name	CMP Development LLC
Therapeutic Classification/ OND Division	DGIEP
Manufacturing Site	(b) (4)
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

Document(s) Assessed	Date Received
eCTD Seq 0000	**03/19/2019**
eCTD Seq 0006	**05/24/2019**
eCTD Seq 0008	**06/11/2019**
eCTD Seq 0012	**07/29/2019**

List Submissions being assessed (table):

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: This is an eCTD submission. (b) (4) Information requests sent on 8 May 2019 and 7 June 2019 and the information request responses received on 24 May 2019, 11 June 2019 and 29 July 2019 are covered in this review.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): N/A

Supporting Documents:
DMF (b) (4) (Type V) – for (b) (4) of the glass vials (LOA from (b) (4)

(b) (4) dated 07 November 2018). Reviewed and deemed adequate in D(b) (4) M04R01.docx, dated 24 April 2019.

DMF (b) (4) – for (b) (4) ated 28 June 2017). Reviewed and deemed adequate in D(b) (4) M15R01.doc, dated 04 March 2019.

S DRUG SUBSTANCE

The drug substance is not reviewed; the drug substance is not provided sterile.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

(Module 3.2.P.1, Description and Composition of Drug Product 0000.pdf)

- **Description of drug product** – clear, colorless, sterile solution. The drug product is supplied in a single strength (3 mM P/mL).

- **Drug product composition** –

Ingredient	Quality Standard	Function	Quantity/mL (mg/mL)
Potassium Phosphate Dibasic	USP	API	300
Potassium Phosphate Monobasic	NF	API	175
WFI	USP	(b) (4)	(b) (4).

- **Description of container closure system** –

Component	Description	Supplier
Vial	(b) (4) mL clear (b) (4) glass	(b) (4)
(b) (4) Stopper	(b) (4)	
Cap	(b) (4)	

Assessment: *Adequate*

The applicant provided an adequate description of the drug product's composition and container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

Container/Closure and Package Integrity

(Module 3.2.P.2, Pharmaceutical Development Report 0000.pdf, pages 93-94/106).

- Test method: Helium Leak Test performed by (b) (4)
- Container Closure System: The test includes the same CCS as proposed for commercial production. The test vials are from lot #7POS001V; therefore, (b) (4)
- The applicant stated that a helium leak rate greater than 10^{-6} cc/sec can be considered a failure for closure integrity and that helium leak rates less than 10^{-6} cc/sec have been associated with acceptable microbial challenge results. The applicant referenced Kirsch, L et al. PDA Journal of Pharmaceutical Science and Technology Vol. 51, No. 5, September-October 1997.
- The CoA provided by (b) (4) for the CCIT results indicates that test method (b) (4) was used; however, the CoA did not include descriptions of the test method, system validation procedures, or positive/negative controls.
- Acceptance criteria:
  - Actual helium leak rate limit for sample vials is ≤ (b) (4) cc/s.
- Results:
  - 20 sample vials from lot # 7POS001V were tested. All actual helium leak rates were (b) (4)

In the Information Request sent on 08 May 2019, the following deficiencies were issued:

1. ***We acknowledge that the Helium Leak Test will be performed for container closure integrity testing (Module 3.2.P.7). However, additional information is needed to assess the acceptability of the protocol. Therefore, address the following:***

   a. ***The test method (b) (4) was referenced for the Helium Leak Test but was not described in the 19 March 2019 submission. Therefore, provide the (b) (4) method document or a description of the test method. The method description should also indicate whether system validation procedures are implemented using certified leak cylinders.***

In their response dated 24 May 2019, the applicant provided a description of the test method as well as the validation report for the subject CCS. The test method

involves introducing helium into the vial, then monitoring the leak rate of helium under vacuum using a helium leak detector equipped with a head-space analysis module. The system is calibrated, and system suitability testing is performed; system suitability testing is described in the Validation Report for Helium Leak Testing 0006.pdf (Seq 0006, Module 3.2.P.7). Briefly, the system is tested using external reference leak standards (b) (4) and helium concentration standards (b) (4) For each reference leak standard and helium concentration standard, six replicate measurements are taken. Acceptance criteria for each test are described in the validation report. A bracketing approach is used to validate the system for multiple vial sizes; the validation report includes data for (b) (4) and (b) (4) vial sizes. All acceptance criteria were met.

b. Provide a description of the positive and negative controls used for the Helium Leak Test and include the relevant results.

The applicant stated that positive and negative controls are not used during the test because a validated method is used for helium leak testing; the validation report was provided.

Assessment: *Adequate*

The applicant stated that positive and negative controls are not used during performance of the helium leak test. Although these controls are generally expected to be included in container closure integrity tests, it was determined that the test method has extensive system suitability requirements and QC standards, including the use of certified helium leak rate standards during each test, that will ensure that the system can accurately measure leaks in the range of (b) (4) std cc/sec. The acceptance criterion of ≤ (b) (4) std cc/sec is acceptable based on a published report correlating helium leak rates with microbial ingress (Kirsch, L et al. *Pharmaceutical Container/Closure Integrity II: the Relationship Between Microbial Ingress and Helium Leak Rates in Rubber Stoppered Glass Vials*. September-October 1997. PDA Journal of Pharmaceutical Science and Technology Vol. 51:195-202) and falls within the range of detection of the leak standards. Additionally, this method has been previously reviewed and deemed adequate in quality microbiology reviews n021382s007r1.doc (dated 01 November 2010; inadequate) and n021382s007r2.doc (dated 25 February 2011; adequate). Therefore, the test method is deemed adequate and additional information will not be requested at this time.

Antimicrobial Effectiveness Testing

Not applicable; the drug product is packaged in a single dose vial.

P.3 MANUFACTURE

P.3.1 MANUFACTURERS

(Module 3.2.P.3.1, Manufacturer for Drug Product 0000.pdf)

(b) (4)

P.3.3 DESCRIPTION OF THE MANUFACTURING PROCESS AND PROCESS CONTROLS

(b) (4)

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The applicant has met regulatory expectations regarding the test method, acceptance criteria and verification of the suitability of the sterility test that will be performed on the product prior to its release.

P.7 CONTAINER CLOSURE

Assessment: See Section P.1.

P.8 STABILITY

P.8.1 STABILITY SUMMARY AND CONCLUSION

(Module 3.2.P.8.1, Stability Summary and Conclusion 0000.pdf)

Stability testing was performed on three drug product batches at long-term (25 ± 2°C/60 ± 5% RH), intermediate (30 ± 2°C/65 ± 5% RH), accelerated (40 ± 2°C/75 ± 5% RH) and alternative long-term condition (5 ± 3°C).
Proposed expiry: 24 months when stored at 5 ± 3°C.

Assessment: *Adequate*

The applicant has met regulatory expectations regarding the proposed expiration date.

P.8.2 POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT

(Module 3.2.P.8.2, Post Approval Stability Protocol and Commitments 0000.pdf)

The product stability specification includes the following microbiological tests:

(b) (4)

Post Approval Stability Commitment

The applicant commits to placing the first three commercial production scale batches in the stability program. Thereafter, on an annual basis, one production batch will be added to the stability program.

Assessment: *Adequate*

The applicant has met regulatory expectations regarding the design of the stability testing program to support the drug product's microbiological quality throughout its shelf life.

P.8.3 STABILITY DATA

(Module 3.2.P.8.3, Stability Data for Exhibit Batches 0000.pdf and Stability Data for Scale Up Batch 0000.pdf)

Stability studies (long-term, intermediate, accelerated and alternative long-term) were performed for lots 7POS001V, 7POS002V, 7POS005V and 18POT001 (scale up batch). The provided results showed that endotoxin and sterility specifications were met.

Assessment: *Adequate*

The stability data submitted to date support the microbiological quality of the subject drug product.

APPENDICES – N/A

R REGIONAL INFORMATION

Executed Batch Records

(Module 3.2.R,

Executed batch records were provided for lots A7POT004V, A7POT005V, A7POT008V and A18POT001. The batch records confirm that (b) (4) processes were used for the manufacture of the exhibit batches.

Assessment: *Adequate*

The applicant has met the regulatory expectations regarding the executed batch records.

Comparability Protocols

None.

Assessment: Not applicable.

2. ASSESSMENT OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1
2.A. Prescribing Information

Storage at 2-8°C.

Route of administration: intravenous injection. The package insert indicated that the drug product is administered "only after dilution and thorough mixing in a larger volume of fluid." A post-dilution hold time is not indicated.

In the Information Request dated 08 May 2019, the following deficiencies were issued:

4. ***We acknowledge that the drug product will be diluted to a "larger volume of fluid" prior to intravenous administration, per the package insert provided in Module 1.14.3.1 of the 25 March 2019 submission. However, the post-dilution storage conditions (i.e. storage temperature and maximum storage time) are not described in the package insert. If the diluted product will be stored for ≥ 4 hours at room temperature and/or ≥ 24 hours under refrigeration, microbiological studies in support of the post-dilution storage conditions should be provided. Please provide a risk assessment summarizing studies that demonstrate adventitious microbial contamination does not grow under the specified storage conditions [(i.e., the number of hours at the proposed temperature(s)]. Reference is made to Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E and Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products, Section 2.2.7. Please include a description of the test methods and results of studies that are designed using a minimum countable inoculum (≤100 CFU/mL) to simulate potential microbial contamination that may occur during product dilution. It is generally accepted that growth is evident when the population increases more than 0.5 $\log_{10}$, however other evidence of growth may be significant. Please perform the test using the storage conditions (i.e. temperature and duration) and diluents specified in product labeling. Please provide***

justification for the selected test conditions and/or diluents as necessary. Periodic intermediate sample times are recommended, as well as extended sample time points demonstrating that the diluted product does not support microbial growth for at least the maximum storage periods under the specified storage conditions. Challenge organisms may include strains described in USP <51> plus typical skin flora, species associated with nosocomial infection, or psychrophilic organisms. Please provide a positive control that demonstrates the viability of the organisms over the duration of the test period.

In their response dated 24 May 2019, the applicant stated that the diluents most often cited for dilution of potassium phosphates are D5W and normal saline. The applicant referenced three databases that support the stability and compatibility of potassium and sodium phosphates admixtures with solutions of dextrose (b) (4) and 5%), sodium chloride ((b) (4) and 0.9%) and various combinations of the two solutions with maximum storage times of 24 to 48 hours at room temperature.

The applicant stated that they initiated two studies to confirm the physical, chemical and microbial stability of the diluted drug product when stored at refrigerated and room temperature for 48 hours. The protocol was provided in the 24 May 2019 submission (Module 3.2.P.8.1, Post-Dilution Microbial Stability Protocol 0006.pdf). The data are anticipated by 08 July 2019 and will be submitted to the Agency by 22 July 2019.

Test conditions: room temperature or refrigerated temperature
Diluents: 5% Dextrose or 0.9% Sodium Chloride
Storage time points: 0, 6, 12, 24 and 48 hours
Test organisms: the microorganisms used in this study are listed and were selected per USP <51>. Each IV bag of diluted drug product is spiked with < 100 CFU/mL

In the Information Request dated 07 June 2019, the following deficiency was issued:

We acknowledge the information provided In Module 3.2.P.8.1 of the 24 May 2019 submission regarding the post-dilution microbial stability protocol. However, the use of positive controls was not indicated. Since positive controls are critical for demonstrating the viability of the test organisms

over the duration of the study, please include positive controls during performance of the post-dilution microbial stability study.

In their response dated 11 June 2019, the applicant acknowledged the need for positive and negative controls, and provided an amended protocol including the controls.

In their 29 July 2019 submission, the applicant provided results for the post-dilution microbial stability study.

(b) (4) Method Suitability Testing

The applicant conducted method suitability testing (called (b) (4) analysis) to demonstrate that the chosen method ((b) (4)) was suitable for the time point assessment and that there was limited microbial inhibition observed in the presence of the sample product. The test was conducted in accordance with USP <51> using a panel of compendial microorganisms. Percent recovery was calculated for the positive controls (no product) and product test samples.

Acceptance criteria: The method is considered suitable if (b) (4) recovery is observed.

Results: The percent recovery for all test samples diluted in either 5% dextrose or 0.9% saline was (b) (4) indicating that the presence of drug product did not negatively affect the viability of the test microorganisms and that the method is suitable for the time point assessment.

Post-dilution Microbial Stability Study

The study design is described above.

Test method: (b) (4)

Positive control: the test microorganisms were inoculated in either 5% dextrose or 0.9% saline and stored at either refrigerated or room temperature. The positive controls were only plated at the T0 time point.

Acceptance criteria: No increase [redacted] at the T6, T12, T24 and T48 time point compared to T0 for any of the test microorganisms [redacted].

Results: No adventitious growth was observed with either diluent after 48 hours storage at refrigerated or room temperature.

Assessment: *Adequate*

Although a positive control was not included during performance of the post-dilution microbial stability study as requested, the applicant provided results for the method validation tests, performed prior to the post-dilution microbial stability study, that verified that the challenge microorganisms were consistently recovered from the test solutions at the proposed storage conditions. Additionally, the positive controls performed at the T0 time point demonstrated the viability of the test microorganisms at the initiation of testing. Therefore, the study methods and results are deemed adequate, and additional information will not be requested at this time.

Post-Approval Commitments

Assessment: For post-approval stability commitment, see Section P.8.2.

MICROBIOLOGY LIST OF DEFICIENCIES

Not applicable.

Primary Microbiology Assessor Name and Date: Laura R. Wasil, Ph.D.; 1 August 2019

Secondary Assessor Name and Date (and Secondary Summary, as needed): Erika Pfeiler, Ph.D.; 1 August 2019

CHAPTER VI: BIOPHARMACEUTICS

Product Information	Potassium Phosphates Injection, USP
NDA Number	NDA 212121
Assessment Cycle Number	1
Drug Product Name/ Strength	Potassium Phosphates Injection, USP 45 mM (3 mM P/mL) is provided as a 15 mL partial fill single-dose vial. It also contains 71 mEq K+ (4.7 mEq K+/mL).
Route of Administration	Intravenous
Applicant Name	CMP Development LLC
Therapeutic Classification/ OND Division	OND/ODEIII/DGIEP
Proposed Indication	Potassium Phosphates Injection is indicated as a source of phosphorus, for addition to large volume intravenous fluids, to prevent or correct hypophosphatemia in patients with restricted or no oral intake. It is also useful as an additive for preparing specific intravenous fluid formulas when the needs of the patient cannot be met by standard electrolyte or nutrient solutions.

Assessment Recommendation: **Adequate**

The Potassium Phosphates Injection, USP 45 mM (3 mM P/mL) developed by CMP Development, LLC (CMP) is a modification of the listed drug (LD) Sodium Phosphates Injection, USP 45 mM (3 mM P/mL), approved under NDA 018892 by HOSPIRA INC. The application is based on a biowaiver for the proposed product. The proposed formulation does not include inactive ingredients.

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 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.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Original	March 19, 2019

S006	May 24, 2019

Highlight Key Issues from Last Cycle and Their Resolution: N/A
Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None

B. 1 Background

Potassium Phosphates Injection is a concentrated sterile solution of Monobasic Potassium Phosphate and Dibasic Potassium Phosphate in Water for Injection. It is indicated as a source of phosphorus and contains the Potassium Phosphate Dibasic and Potassium Phosphate Monobasic at (b) (4) and (b) (4) The current proposed formulation is a potassium salt while the LD is a sodium salt; in addition, ratio of the monobasic and dibasic is not at the same ratio/concentration as the approved (NDA 018892) reference listed drug (LD) Sodium Phosphates Injection, USP 45 mM (3 mM P/mL). However, the total Phosphate composition is 45 mM/15 mL (3 mM P/mL) which is same as the reference listed drug based on the calculation provided below.

(b) (4)

It contains no bacteriostatic agent or other preservative and is supplied in a partial fill (15 mL) single dose vial. The concentrated solution is administered by intravenous route only after dilution into large volume intravenous fluids. Intermittent infusion doses of Potassium Phosphates Injection are typically prepared in 100 to 250 mL of Normal Saline (0.9% Sodium Chloride Injection USP) or D5W (5% Dextrose Injection USP) and infused over a range of 2 to 12 hours.

The Sponsor proposed to rely on the Agency's previous finding of safety and efficacy of the listed drug Sodium Phosphates Injection, NDA 18892 approved in 1983 as well as published literature and data generated by the Sponsor, to satisfy the 505(b)(2) regulatory requirements for the Potassium Phosphates Injection, USP formulation. Potassium Phosphates Injection, USP provides the same phosphate concentration and will be administered at the same dosage level, for the same duration, and for the same indication as the listed drug Sodium Phosphates Injection, 3mM P/mL. No clinical safety and efficacy or pharmacokinetic studies were conducted in support of this 505(b)(2) Application. The establishment of adequate bridging to the listed drug serves as a clinical surrogate for NDA approvability decision making.

The Sponsor claims that as both Potassium Phosphates Injection, USP, and the LD are in aqueous solutions, contains same amount of total phosphates, are injected

intravenously, their bioequivalence is self-evident. Therefore, the biobridge between the proposed and the LD can be adequately established.

- The focus of the biopharmaceutics review was the assessment of adequate bridging of the proposed drug product to the listed drug and the following **information request dated May 9, 2019** was conveyed to the Applicant:

You plan to use Hospira's Sodium Phosphates Injection, USP 45 mM approved under NDA018892 (06/02/2005) as your listed drug. For that purpose, you need to establish a biobridge as per 21 CFR 320.24(b)(6) between your proposed product and other product/s in absence of any PK study. Explain how you intend to pursue that in terms of both Phosphates and Potassium contents. Your response needs to be supported with physicochemical (e.g., side-by side comparison of the formulations, pH, osmolality etc) and any other relevant data.

In the response dated May 24, 2019 to the agency information request dated May 8, 2019, the sponsor provided the following table comparing the proposed product and the reference product:

Parameter	Potassium Phosphates Injection	Sodium Phosphates Injection (Hospira)
Formulation	300 mg/mL of potassium phosphate dibasic, (b) (4) and 175 mg/mL of potassium phosphate monobasic, (b) (4)	142 mg/mL of sodium phosphate dibasic, anhydrous and 276 mg/mL of sodium phosphate monobasic, monohydrate
millimoles of Phosphorous per mL	3	3
mEq of Cation per mL	4.7 (K^+)	4 (Na^+)
Osmolarity (mOsmol/mL) (calculated)	7.7	7
pH	6.9 (6.5 – 7.5)	5.5 (5.0 – 6.0)
Bacteriostat agent	None	None
Antimicrobial agent	None	None
Buffer	None	None

Taking into account the sponsor's response and other information provided in the submission, overall biopharmaceutics information of this submission are summarized below:

- The are no inactive ingredients in the proposed product.
- The pH, calculated ionic strength as well as measured osmolality of the proposed drug product are not identical to that of the listed drug.

- The viscosity of both formulation was not presented, however the composition as listed and due to absence of inactive ingredients, the viscosity is expected to be identical.
- The pH difference is attributed to the difference in the ratio of the monobasic and dibasic phosphate ratio. The normal pH range of a monobasic and dibasic phosphate salt is 5.8 to 7.4. Since the millimoles of phosphates (active moiety) is same between the formulations and the concentrated solution will administered by the intravenous route only after dilution into large volume intravenous fluids, the slight difference in the pH of the proposed product with respect to the reference product will not have any clinical significance.
- For the same reason as cited above, the minor differences noted in terms of ionic strength and osmolality are considered to have very limited clinical significance.

B. 2 BIOWAIVER REQUEST
Assessment: ***{Adequate}***

- Based on the information provided, consistent with 21 CFR 320.24. (b)(6), FDA deemed the information supporting the relative bioavailability of the proposed drug product to the listed drug 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.
- Overall, the application is acceptable from Biopharmaceutics perspective.

B.3 Other Relevant Information

- Of note, other than total phosphates, the role and K+ in place of Na+ needs to be addressed clinically. Potassium phosphates may be safely used in patients with serum potassium level below 4 mg/dL. CMP Development's Potassium Phosphates Injection USP contains 4.7 mEq of potassium/mL as compared to 4.4 mEq of potassium/ml in the currently unapproved products. According to the information provided in the submission, to treat hypophosphatemia in patients, currently unapproved products containing 4.4 mEq of potassium/ml was used. However, the serum potassium concentrations did not change to a clinically significant degree compared to the use of the proposed product containing 4.7 mEq of potassium/ml. Therefore, CMP Development's Potassium Phosphates Injection USP, despite having a slightly higher potassium content, should demonstrate similar safety findings especially when administered to patients with a pre-dose serum potassium < 4.0 mmol/L and in whom routine serum potassium monitoring is conducted. The maximum daily dose of Potassium Phosphates Injection developed by CMP to be administered per day for an adult is limited to 15-mL (one vial). This equates to 70.5 meq K+ and 45 mM P per 24 hours. The concomitant amount of potassium (K+ 4.7 mEq/mL) must be calculated into total electrolyte dose of such prepared solutions. The clinical review and labeling should address that.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Biopharmaceutics Assessor's Name and Date:
Sarah Ibrahim, Ph.D. May 26, 2019
Secondary Assessor Name and Date (and Secondary Summary, as needed):
Tapash Ghosh, Ph.D.

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment – NDA 212121

a) Drug Product: Potassium Phosphates Injection, 45 mmol Phosphorus/15 mL (3 mmol Phosphorus/mL)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Aluminum Content	API, glass vial and pH of the solution	M	(b) (4)	(b) (4) None	None
Particulate Matter in admixture with TPN	Potential formation of calcium phosphate precipitates.	H to M		(b) (4) Low	None
Bioburden	Manufacturing environment and processes	M		(b) (4) Low	None
Sterility	Sterilization	M		(b) (4) Low	None