

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206814Orig1s000

OTHER REVIEW(S)



Division of Cardiovascular and Renal Products

Original NDA: 206814

Sponsor: Pharma-Med, Inc.

Purpose of Memo: Discuss rationale for preliminary label changes

Product: Potassium Chloride Oral Solution, USP, 1.3 mEq/ mL, 2.6 mEq/mL

Proposed Indication: Treatment of patients with hypokalemia, with or without metabolic alkalosis; [REDACTED] (b) (4)

[REDACTED] (b) (4)

Date of Submission: 2/27/2014

Date Completed: 1/5/2015

Medical Officer: Melanie J. Blank, MD

Team Leader: Martin Rose, MD

Division Director: Norman Stockbridge, MD, PhD,

1 Background

1.1 Introduction and Regulatory History

On February 27, 2014, Pharma-Med, Inc. submitted a 505(b)(2) New Drug Application for a 10% potassium chloride oral solution (20 mEq/15 ml) and a 20% potassium chloride oral solution (40 mEq/15 ml). The reference listed drug (RLD) is potassium chloride extended release tablets (K-Dur 10 and 20 mEq) under NDA 019439. Liquid oral potassium chloride at these strengths is a marketed but nonapproved drug product.

The submission included a request for waiver of *in vivo* bioavailability studies based on: (1) published literature on clinical studies that compared the bioavailability of potassium chloride (KCl) tablets and oral solution and (2) major excipients used in the proposed solution formulation are GRAS (generally recognized as safe). The applicant also referenced clinical studies with KCl solution used for demonstrating extended release versus immediate release characteristics of formulations from two previous NDAs (RLD NDA 019439 and NDA 019123). The clinical pharmacology review by Dr. Sabarinath stated that, "The results from the studies described above show that the bioavailability

of KCl, as measured by the cumulative urinary excretion of K⁺ over a 24 hour post dose period, is comparable across the liquid formulation and various types of modified release (potassium chloride) products.” While absorption was faster with the liquid product, Dr. Sabarinath did not think that this posed a clinically relevant concern. I concur with Dr. Sabarinath. Also, the liquid formulation caused fewer lesions in the upper gastrointestinal tract than KCl tablets although other gastrointestinal disturbances (abdominal pain, nausea and diarrhea but *no* gross or occult bleeding) occurred more frequently with the liquid. Thus, there were no concerning safety issues. From a bioequivalence perspective, Dr. Sabarinath concluded that the proposed oral solution of KCl could be approved for use as the sponsor proposes.

On 4/3/2014 the Sponsor submitted a request for a waiver of the pediatric studies required under the Pediatric Research Equity Act (PREA). However, the sponsor submitted literature to support safety and effectiveness in the pediatric population and therefore, the waiver was deemed to be unnecessary. The pediatric literature (see 2.5) supports the extrapolatability of safety and effectiveness of liquid oral KCl in children of all ages. On December 17, 2014, the Pediatric Review Committee (PeRC) and Better Pharmaceuticals for Children Act (BPCA) /Initial Pediatric Study Plan (iPSP) subcommittees met and agreed that the PREA requirements have been met.

2 Labeling and Preliminary Label Changes

2.1 Initial Approval

The initial approval of any KCl product was 1948, not 1975 as stated in the applicant's original label proposal.

2.2 Indication

The following changes to Section 1 were proposed [REDACTED] (b) (4)

“Potassium Chloride is indicated for the treatment and prophylaxis of hypokalemia in patients for whom dietary management with potassium-rich foods and/or diuretic dose reductions are insufficient.”

Rationale: Digitalis toxicity should be treated individually. While it might be acceptable to treat most cases of digitalis toxicity with KCl, there are exceptions making a simple indication statement inadvisable. Each case of digitalis toxicity should be considered individually for the need for KCl replacement. The following paragraph which was extracted from a publication on digitalis toxicity [REDACTED] Potassium repletion in the presence of low or low normal serum potassium levels is the initial therapy of choice for ectopic rhythms. Potassium supplementation generally is contraindicated in the presence of renal failure, hyperkalemia, or depressed AV conduction (greater than first degree AV

Patients with periodic hypokalemic paralysis constitute a small subsegment of the population of patients with hypokalemia.³

2.3 Administration and Monitoring

The following additions to Section 2 were proposed:

“If serum potassium concentration is < 2.5 mEq/L, use intravenous potassium instead of oral supplementation.⁴⁵”

Monitoring

Monitor serum potassium and adjust dosages accordingly. For treatment of hypokalemia, potassium levels should be monitored daily or more often depending on the severity of hypokalemia until they return to normal. Monitor potassium levels monthly to biannually for maintenance or prophylaxis.

The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance, volume status, electrolytes, including magnesium, sodium, chloride, phosphate, and calcium, electrocardiograms and the clinical status of the patient. Correct volume status, acid-base balance and electrolyte deficits as appropriate.

Adult Dosing

Treatment of hypokalemia:

Daily dose range from 40 to 100 mEq. Give in 2 to 5 divided doses: limit doses to 40 mEq per dose. The total daily dose should not exceed 200 mEq in a 24 hour period.

Maintenance or Prophylaxis,

Typical dose is 20 mEq per day. Individualize dose based upon serum potassium levels.

¹ Bhatia J, (1987) Digitalis toxicity: mechanisms, diagnosis, and management. *Jl of Card Surg*, Vol 2: 4, p. 453-65.

² Levitt, Jacob O, (2008) Practical aspects in the management of hypokalemic periodic paralysis, *Journal of Translational Medicine*, Vol 6:18, doi:10.1186/1479-5876-6-18

³ Vikart, S. et al (2002), Hypokalemic Periodic Paralysis, Gene Review, NCBI Bookshelf.

⁴ Hemstreet, BA, (2006), Potassium and phosphorus repletion in hospitalized patients: implications for clinical practice and the potential use of healthcare information technology to improve prescribing and patient safety, *Current Medical Research and Opinion*, vol. 22: 12, 2449–2455.

⁵ Asmar, A, et al, (2012) A Physiologic-Based Approach to the Treatment of a Patient With Hypokalemia, *Am J Kidney Dis*. 60:3,492-497.

Studies support the use of potassium replacement in digitalis toxicity. When alkalosis is present, normokalemia and hyperkalemia may obscure a total potassium deficit. The advisability of use of potassium replacement in the setting of hyperkalemia is uncertain.⁶

Pediatric Dosing

Treatment of hypokalemia:

Pediatric patients aged birth to 16 years old: 2 to 4 mEq/kg/day in divided doses; not to exceed 1mEq/kg as a single dose or 40 mEq whichever is lower; maximum daily doses should not exceed 100 mEq. If deficits are severe or ongoing losses are great, consider intravenous therapy.^{7, 8, 9, 10}

Maintenance, or Prophylaxis

Pediatric patients aged birth to 16 years old: Typical dose is 1 mEq/kg/day. Do not exceed 3 mEq/kg/day.”^{7, 8, 9, 10,}

Rationale: More specific instructions on how and when to use oral products, how and when to monitor and additional patient care instructions were supported by the literature.

2.4 Drug Interactions

Addition of the following language to section 7 is proposed:

Angiotensin Receptor Blockers

Use with angiotensin receptor blockers (ARBs) produces potassium retention by inhibiting aldosterone production. Potassium supplements should be given to patients receiving ARBs only with close monitoring.

Rationale: Literature supports this potential drug interaction.^{11, 12}

⁶ Brater, DC and Morelli, HF (1977) *Jl of Clin Pharm and Ther*, Vol, 22: 1 , p. 21-33.

⁷ Taketomo, CK et al (2014), *Pediatric & Neonatal Dosage Handbook*, American Pharmacists Association, 21st edition, Lexi-Comp, p. 1708-1709

⁸ Tschudy M, Arcara K, editors. (2012) *The Harriet Lane Handbook :a manual for pediatric house officers / the Harriet Lane Service, Children's Medical and Surgical Center of the Johns Hopkins Hospital*. 19th ed. Philadelphia, PA: Elsevier Mosby; Chapter 11, Fluids and Electrolytes, p.283. Chapter 29, Drug Doses, p.917-918.

⁹ Kliegman R, Nelson, et al, editors. *Nelson textbook of pediatrics*. 19th ed. Philadelphia, PA: Elsevier/Saunders; 2011. Chapter 52, Electrolyte and Acid-Base Disorders, 52.4 Potassium, p.219-225.

¹⁰ Rudolph, C, editor. *Rudolph's pediatrics*. 22nd ed. New York: McGraw Hill Medical; 2011. Chapter 466, Fluid, Electrolyte, and Acid-Base Disorders, p.1677-83.

¹¹ Park LW, et al, (2014), *Jl of Clin Pharm and Ther*, Vol. 39, 61-68.

¹² Raebel, M. (2012) Hyperkalemia Associated with Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers, *Cardiovascular Therapeutics*, Vol 30, e156–e166.

2.5 Pediatric Use

The following language for section 8.3 is proposed:

The safety and effectiveness of potassium chloride has been demonstrated in children with diarrhea and malnutrition from birth to 18 years.

Rationale: Literature supports pediatric use of oral liquid potassium chloride.^{7,8, 9, 10, 13,14,15}

¹³ Mahalanabis D et al, (1995) Hypotonic oral rehydration solution in acute diarrhoea: a controlled clinical trial. *Acta Paediatr.*;84(3):289-93.

¹⁴ Nalin DR, et al (1980). Comparison of low and high sodium and potassium content in oral rehydration solutions. *J Pediatr.* Vol:97:5, p.848-53.

¹⁵ Manary, MJ and Brewster (1997), Potassium Supplementation in Kwashiorkor, *Jl of Ped Gastro and Nutr.*, Vol 24, p. 194-201.

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/s/

MELANIE J BLANK
01/08/2015

RHPM NDA Overview
December 22, 2014

Potassium Chloride Oral Solution, 20 mEq/15 mL, 40 mEq/15 mL

NDA 206814

Applicant: Pharma-Med, Inc.
Classification: 7 (Already Marketed Drug without Approved NDA)
Review Classification: Standard (12 month review)
Proposed Indication: treatment of hypokalemia
Date of Application: February 27, 2014
Receipt Date: February 27, 2014
User Fee Goal Date: December 27, 2014

REVIEW TEAM

Office of New Drugs, Office of Drug Evaluation I, Division of Cardiovascular and Renal Products

- Division Director
 - Norman Stockbridge, M.D., Ph.D
- Medical Reviewer
 - Melanie Blank, M.D.
- Regulatory Health Project Manager
 - Edward Fromm, R.Ph., RAC

Office of New Drug Quality Assessment (ONDQA), Branch 1

- Cross Discipline Team Leader
 - Kasturi Srinivasachar, Ph.D.
- Review Chemist
 - Mohan Sapru, Ph.D.

Office of New Drug Quality Assessment (ONDQA)

Product Quality Microbiology Reviewer

- Denise Miller, Ph.D.

Biopharmaceutics Reviewer

- Sandra Suarez Sharp, Ph.D.

Office of Clinical Pharmacology

- Sreedharan Sabarinath, PhD,

BACKGROUND

This is a 505(b)(2) NDA for potassium chloride oral solution, 20 mEq/15mL and 40 mEq/15 mL. Although potassium chloride has been previously approved in other dosage forms – injection and extended release tablets or capsules, the oral solution is a new dosage form which has been marketed but never approved. This filing is based upon the reference listed drug (RLD), K-DUR, potassium chloride extended release tablets, NDA 19439 approved in 1986.

User Fee

The applicant received a small business waiver for the user fee.

Pediatrics

Literature references supplied by the applicant support use in pediatrics, from birth to 16 years of age. The application was reviewed by the PeRC committee on December 17, 2014. PeRC had several comments/recommendations:

- The PeRC agreed with the assessment presented for all pediatric patients ages for the proposed indications.
- The PeRC also recommends that the dosage and administration section be modified to include appropriate dosing in mEq/kg for all pediatric age ranges.

Trade name

The applicant did not apply for a tradename for the product.

REGULATORY TIMELINE

- Pre-IND meeting, June 20, 2012

REVIEWS

Divisional Memorandum (dated December 22, 2014)

Dr. Stockbridge recommends approval of potassium chloride oral solution.

Cross-Discipline Team Leader (CDTL) Review (dated December 12, 2014)

Dr. Srinivasachar recommends that Potassium Chloride Oral Solution, 20mEq/15mL and 40mEq/15mL be approved with an expiration dating period of 24 months when stored at room temperature. The Approval letter should include appropriate language for the Post Marketing Commitment agreed to by the Applicant for antimicrobial preservative effectiveness testing of the 40mEq/15mL formulation.

Medical Reviews

Dr. Blank did not do a formal medical review, but did edit substantial sections of the labeling that were outdated. She did a formal determination of the proposed withdrawal of the RLD for this application, NDA 19439, was not due to reasons of safety or efficacy.

- **Financial** – N/A, as there were no clinical studies for review.

Biostatistics Review –N/A

Clinical Pharmacology Review (dated October 9, 2014)

Dr. Sabarinath recommended approval based on the results of studies that showed that the bioavailability of potassium chloride, as measured by the cumulative urinary excretion of K⁺ over a 24 hour post dose period, is comparable across the liquid formulation and various types of modified release products. It was also concluded from these studies that the overall gastrointestinal tolerance to potassium chloride can be considered to be at least similar for the liquid and modified release products.

Pharmacology and Toxicology Review –N/A

Office of New Drug Quality Assessment (ONDOA)

- **CMC Review** (dated October 27 and December 9, 2014)
Dr. Sapru recommended approval of the NDA from a CMC perspective.
Drug Substance: The Applicant referenced DMF (b)(4) for complete information on the drug substance, potassium chloride. The reviewer states that the original DMF has been reviewed and found to be adequate.
Drug Product: The product will be marketed in two strengths, 20 mEq/15 mL and 40 mEq/15mL. The excipients in the formulation include glycerin, propylene glycol, methylparaben, propylparaben, sucralose, citric acid, natural and artificial orange flavor, FD&C Yellow #6 and purified water.. The drug product is packaged in (b)(4) mL white HDPE bottles with (b)(4). The specification has been revised to include a test for pH with limits between 3.0 and 6.5 based on the reviewer's recommendation. An expiration dating period of 24 months has been requested by the Applicant and is granted for both strengths based on the stability data provided.
Facilities review/inspection: The drug substance and drug product manufacturing sites were submitted for inspection and the current overall Office of Compliance recommendation is "Acceptable".
- **Biopharmaceutics Review** (dated October 10, 2014)
Dr. Suarez recommends approval from a Biopharmaceutics perspective. She concluded that the provided formulation and PK information support the bridging of the proposed product and the products used in the published pharmacokinetic literature and therefore a biowaiver for the proposed product could be granted.
- **Product Quality Microbiology Review** (dated October 24, 2014)
Dr. Miller recommended approval from a quality microbiology perspective but requested that the antimicrobial preservative effectiveness testing be also performed, post approval, on the second formulation (40mEq/mL). The Applicant has committed to conduct this testing.
- **Environmental Assessment**
 - Categorical exclusion granted (see Dr. Sapru's review)

CONSULTS

DMEPA Review (dated October 24 and November 19, 2014)

Dr. Stewart had labeling recommendations for the immediate container labels which the applicant agreed to in a submission date October 30, 2014

Office of Prescription Drug Promotion (dated December 19, 2014)

Dr. Shah finalized her review and included a number of labeling comments in her review.

505(b)(2) Clearance

The 505(b)(2) clearance committee, in an e-mail dated November 26, 2014 said the application was cleared for action from a 505(b)(2) perspective with the caveat that the RLD, NDA 19439 was not being withdrawn for reasons of safety or effectiveness.

ADL Review

Mr. Monteleone edited substantial sections of the labeling that were outdated and also revised it to be PLR compliant.

CONCLUSION

An approval letter was issued for this application and signed by the Division Director, Norman Stockbridge, M.D., Ph.D., on December 22, 2014. The approval letter with PMC, was appended with the agreed-upon labeling text and immediate container labels.

Edward J. Fromm, R.Ph., RAC
Regulatory Health Project Manager

dr-ef-12/22/14

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/s/

EDWARD J FROMM
12/29/2014



DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Divisional Memo

NDA: 206814 Potassium chloride oral solution.

Sponsor: Pharma-Med

Review date: 22 December 2014

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

This memo conveys the Division's recommendation to issue an "Approval" letter for this application.

This application has been the subject of reviews of CMC (Sapru; 27 October and 9 December 2014), biopharmaceutics (Sharp; 16 October 2014), microbiology (Miller; 24 October 2014), and clinical pharmacology (Sabarinath; 9 October 2014). There is also a CDTL memo (Srinivasachar; 12 December 2014), with which I am in complete agreement.

The applicant seeks to market oral solutions of KCl at 20 or 40 mEq/15 mL. The approval pathway is 505(b)(2), relying upon the Agency's findings for intravenous and other oral dosage forms. There is neither a non-clinical nor a clinical review.

There are no manufacturing issues and manufacturing facilities have been deemed satisfactory.

Microbiology seeks information on antimicrobial effectiveness as a post-marketing commitment, which has been negotiated with the sponsor.

Labeling has been fully negotiated. There are no remaining approval issues.

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/s/

NORMAN L STOCKBRIDGE
12/22/2014

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 206814
Product Name: Potassium Chloride Oral Solution, 20 mEq/15 mL and 40 mEq/15 ml

PMR/PMC Description: Antimicrobial Effectiveness Testing (AET) for Potassium Chloride Oral Solution, 40 mEq/15ml

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>N/A</u>
	Study/Trial Completion:	<u>N/A</u>
	Final Report Submission:	<u>03/31/2015</u>
	Other: <u>N/A</u>	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The finished drug product has a microbial limit specification, but the Microbiology reviewer wants Antimicrobial Effectiveness Testing (AET) on the 40 mEq/15 ml strength. The reviewer believes that the risk to the patient is minimal, and thus the testing can be done post-approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Antimicrobial Effectiveness Testing (AET) was completed on the 20 mEq/15 ml product but not the 40 mEq/15 ml strength. The testing requested by the sponsor will confirm the effectiveness of the preservative system.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Antimicrobial Effectiveness Testing (AET) on the 40 mEq/15 ml strength of Potassium Chloride Oral Solution.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Antimicrobial Effectiveness Testing (AET) was completed on the 20 mEq/15 ml product but not the 40 mEq/15 ml strength. The testing requested by the sponsor will confirm the effectiveness of the preservative system.

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

Antimicrobial Effectiveness Testing (AET) on the 40 mEq/15 ml strength by March 31, 2015. The completed study is to be submitted to the Agency as a CBE-0 supplement.

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/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.

(signature line for BLAs)

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/s/

Lori A WACHTER
12/17/2014

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

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

Memorandum

Date: August 15, 2014

To: Russell Fortney
Regulatory Project Manager
Division of Cardiology and Renal Products (DCRP)

Edward Fromm
Chief, Project Management Staff, DCRP

From: Puja Shah, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 206814
POTASSIUM CHLORIDE ORAL SOLUTION

Background

This consult review is in response to DCRP's August 13, 2014, request for OPDP's review of the draft package insert (PI) for POTASSIUM CHLORIDE ORAL SOLUTION. OPDP reviewed the substantially complete version of the draft PI provided on December 8, 2014. Our comments on the PI are included directly on the attached copy of the labeling.

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Puja Shah at 240-402-5040 or puja.shah@fda.hhs.gov

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/s/

PUJA J SHAH
12/19/2014

LABEL AND LABELING MEMO

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

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

Date : November 19, 2014

Requesting Office or Division: Division of Cardiovascular & Renal Products (DCRP)

Application Type and Number: NDA 206814

Product Name and Strength: Potassium Chloride Oral Solution, USP
20 mEq per 15 mL and 40 mEq per 15 mL

Product Type: Single Ingredient Product

Rx or OTC: Rx

Applicant/Sponsor Name: Pharma-Med, Inc.

Submission Date: October 30, 2014

OSE RCM #: 2014-478-1

DMEPA Primary Reviewer: Janine Stewart, PharmD

DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 INTRODUCTION

This memorandum evaluates the revised container labels for Potassium Chloride Oral Solution, USP 20 mEq per 15 mL and 40 mEq per 15 mL, NDA 206814, submitted on October 30, 2014. DMEPA previously reviewed the proposed labels and labeling under OSE Review # 2014-478 dated October 24 2014.

2 MATERIAL REVIEWED

DMEPA reviewed the revised container labels submitted on October 30, 2014. We compared the revised container labels against the recommendations contained in OSE Review # 2014-478 dated October 24, 2014 (See DARRTS NDA 206814 Labeling Review dated 10/24/2014).

3 CONCLUSIONS AND RECOMMENDATIONS

The revised container labels adequately address our concerns from a medication error perspective. We have no additional comments at this time.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Cherye Milburn, at 301-796-2084.

Each 15 mL (tablespoon) contains:
Potassium
Chloride, USP 20 mEq

Inactive ingredients: citric acid,
FD&C Yellow #6, glycerin,
methylparaben, natural/artificial
orange flavor, propylene glycol,
propylparaben, purified water,
sodium citrate dihydrate, sucralose.

Dosage and Administration: See
accompanying prescribing
information.

Store at 25°C (77°F); excursions
permitted to 15°-30°C (59°-86°F).

KEEP THIS AND ALL MEDICA-
TION OUT OF THE REACH OF
CHILDREN.

Manufactured by:
Lehigh Valley Technologies, Inc.
Allentown, PA 18102

NDC 64950-320-47

Potassium Chloride Oral Solution, USP, 10%

20 mEq per 15 mL

**DILUTE PRIOR TO
ADMINISTRATION**

Rx Only 473 mL



Lot No.:
Exp. Date:

Rev. 10/14



Lehigh Valley Technologies, Inc.

Each 15 mL (tablespoon) contains:
Potassium
Chloride, USP 40 mEq

Inactive ingredients: citric acid,
FD&C Yellow #6, glycerin,
methylparaben, natural/artificial
orange flavor, propylene glycol,
propylparaben, purified water,
sodium citrate dihydrate, sucralose.

Dosage and Administration: See
accompanying prescribing
information.

Store at 25°C (77°F); excursions
permitted to 15°-30°C (59°-86°F).

KEEP THIS AND ALL MEDICA-
TION OUT OF THE REACH OF
CHILDREN.

Manufactured by:
Lehigh Valley Technologies, Inc.
Allentown, PA 18102

NDC 64950-322-47

Potassium Chloride Oral Solution, USP, 20%

40 mEq per 15 mL

**DILUTE PRIOR TO
ADMINISTRATION**

Rx Only 473 mL



Lot No.:
Exp. Date:

Rev. 10/14

L V T Lehigh Valley Technologies, Inc.

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/s/

JANINE A STEWART
11/19/2014

CHI-MING TU
11/19/2014

LABEL AND LABELING REVIEW

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

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

Date of This Review: October 24, 2014
Requesting Office or Division: Division of Cardiovascular & Renal Products (DCRP)
Application Type and Number: NDA 206814
Product Name and Strength: Potassium Chloride Oral Solution, USP
20 mEq per 15 mL and 40 mEq per 15 mL
Product Type: Single Ingredient Product
Rx or OTC: RX
Applicant/Sponsor Name: Pharma-Med, Inc.
Submission Date: February 27, 2014
OSE RCM #: 2014-478
DMEPA Primary Reviewer: Janine Stewart, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

As part of the approval of this new drug application, this review evaluates the proposed container label and Prescribing Information for Potassium Chloride Oral Solution, USP, 20 mEq per 15 mL and 40 mEq per 15 mL, for areas of vulnerability that can lead to medication errors.

1.1 REGULATORY HISTORY

Potassium Chloride Oral Solutions, USP, 10% (20 mEq per 15 mL) and 20% (40 mEq per 15 mL), have been marketed as unapproved products. On February 27, 2014, the Applicant, Pharma-Med, Inc. submitted a 505(b)(2) NDA for Potassium Chloride Oral Solution, USP, 20 mEq per 15 mL and 40 mEq per 15 mL to be manufactured by Lehigh Valley Technologies, Inc. The listed drug (LD) is K-Dur® (potassium chloride extended-release tablets), 10 mEq and 20 mEq, under NDA 019439.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study	D- N/A
ISMP Newsletters	E
Other	F- N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Although no medication errors were identified that were relevant to this review, we performed a risk assessment of the proposed Prescribing Information (PI) and container labels to identify deficiencies that may lead to medication errors and areas for improvement. After careful review of the proposed PI, we noted a few instances of the use of trailing zeroes in the proposed PI. Numbers containing decimal points in measurement can lead to ten-fold dosing errors when the decimal point goes unseen. To minimize such errors, such statements should be presented in whole numbers, and not with a decimal point that is followed by a terminal

zero.^{1,2} In addition, there is product information that can be revised, removed, or relocated to improve the readability of product information that is important for the safe use of this product.

DMEPA carefully reviewed the proposed container labels for Potassium Chloride Oral Solution, USP, 20 mEq per 15 mL and 40 mEq per 15 mL and noted the omission of a statement that notifies the user of an important step in the safe administration of this product. Therefore, we provide recommendations in Section 4 in order to promote the safe use of this product.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase clarity, readability, and the prominence of important information to promote the safe use of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

Based on this review, we recommend the following revisions to the proposed Prescribing Information (PI) as detailed below for review and consideration by DCRP. See Appendix G for tracked change edits in the proposed PI.

Prescribing Information

1. Trailing zeroes are error-prone and can result in ten-fold error of measurement if the decimal is not seen (i.e. '1.0' can be misinterpreted as '10'); thus, we recommend removing the use of trailing zeroes where they appear in the PI.
2. In the Dosage and Administration sections of the Highlights of PI and the Full PI, the statement "The usual dietary potassium intake by the average adult..." may be misinterpreted as the recommended dose for Potassium Chloride Oral Solution. While we acknowledge that this exact statement appears in the same sections of the PI for the listed drug K-Dur, there is concern that this statement could lead to dosing errors.

¹ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2013 [cited 2013 Sep 16]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>.

² Guidance for Industry (draft): Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. April 2013. Accessed online on October 23, 2014 at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>

3. In the Dosage and Administration section of the Full Prescribing Information, the statement, “Important: The contents of the oral solution...” is ambiguous. Please revise the statement to read similar to: “This preparation, like all potassium supplements, must be properly diluted to avoid the possibility of gastrointestinal irritation. Each dose should be diluted with at least 4 ounces of cold water. The dose should also be taken with meals or immediately after eating.” Consider relocating this information to a new sub-section “2.1 Important Administration Instructions” to the Dosage and Administration section to highlight this important administration information.

4.2 RECOMMENDATIONS FOR PHARMA-MED, INC.

Container Labels

1. Add the statement “Dilute prior to administration” to the principal display to highlight this important administration information for the safe use of this product.
2. Remove the statement located on the side panel [REDACTED] (b) (4)
[REDACTED]
[REDACTED] t.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Potassium Chloride Oral Solution, USP that Pharma-Med, Inc. submitted on February 27, 2014, and the listed drug (LD).

Table 2. Relevant Product Information for Potassium Chloride Oral Solution and the Listed Drug		
Product Name	Potassium Chloride Oral Solution, USP	Potassium Chloride Extended Release Tablets, USP (NDA 019439)
Initial Approval Date	N/A	June 13, 1986
Active Ingredient	Potassium Chloride	Potassium Chloride
Indication	<p>1. For the treatment of patients with hypokalemia with or without metabolic alkalosis (b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p>	<p>1. For the treatment of patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication, and in patients with hypokalemic familial periodic paralysis.</p> <p>2. For the prevention of hypokalemia in patients who would be at particular risk if hypokalemia were to develop, e.g., digitalized patients or patients with significant cardiac arrhythmias.</p>
Route of Administration	Oral	Oral
Dosage Form	Solution	Extended-Release Tablet
Strength	10%: 20 mEq per 15 mL 20%: 40 mEq per 15 mL	10 mEq and 20 mEq
Dose and Frequency	<p>Dosage is adjusted to the needs of the individual. Typical doses are:</p> <p>Treatment: 40 mEq to 100 mEq in divided doses so that no more than 20 mEq is given in a single dose</p>	<p>Dosage is adjusted to the needs of the individual. Typical doses are:</p> <p>Treatment: 40 mEq to 100 mEq in divided doses so that no more than 20 mEq is given in a single dose</p>

	Prevention: 20 mEq once daily.	Prevention: 20 mEq once daily.
How Supplied	473 mL bottles	10 mEq: 100-count bottle 20 mEq: 100-count bottle & 1000-count bottle
Storage	Store at room temperature, 25°C (77°F); excursions permitted to 15°C - 30°C (59°F - 86°F). Protect from light.	Store at room temperature, 25°C (77°F); excursions permitted to 15°C - 30°C (59°F - 86°F).
Container Closure	(b) (4) White HDPE bottle (b) (4)	HDPE bottle with child-resistant closure.

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on October 9, 2014 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter²

Date Range	October 1, 2009 to October 1, 2014
Product	Potassium Chloride [active ingredient] Potassium 10% Liquid; Potassium 20% Liquid [product verbatim]
Event (MedDRA Terms)	Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Quality Issues (NEC)[HLT]

B.2 Results

Our search identified 326 cases. These results included many forms of potassium chloride including intravenous solutions, oral tablets, oral powders, and multi-ingredient products containing potassium chloride such as bowel preparation products and parenteral nutrition. We attempted to identify cases specifically involving potassium chloride oral solution. After applying text narrative searches using the terms Oral Solution, Oral Liquid and Potassium Solution, we narrowed the results to 7 cases of which 0 (zero) described errors relevant for this review.

B.3 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L: Drive on October 1, 2014 using the terms, Potassium Chloride Oral Solution to identify reviews previously performed by DMEPA.

C.2 Results

Our search identified 0 (zero) previous reviews.

APPENDIX E. ISMP NEWSLETTERS

E.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on October 1, 2014 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community, and Nursing
Search Strategy and Terms	Match Exact Word or Phrase: Potassium Chloride Oral Solution

E.2 Results

Our search identified 1 (one) article that was not relevant for this review.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,³ along with postmarket medication error data, we reviewed the following Potassium Chloride Oral Solution, USP labels and labeling submitted by Pharma-Med, Inc. on February 27, 2014.

- Container label
- Full Prescribing Information

G.2 Label and Labeling Images



³ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANINE A STEWART
10/24/2014

CHI-MING TU
10/24/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 206814 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: potassium chloride Dosage Form: oral solution Strengths: 20 mEq/15 mL and 40 mEq/15 mL		
Applicant: Pharma-Med, Inc Agent for Applicant (if applicable): Melissa Goodhead		
Date of Application: February 27, 2014 Date of Receipt: February 27, 2014 Date clock started after UN: N/A		
PDUFA Goal Date: December 27, 2014	Action Goal Date (if different): N/A	
Filing Date: 4/25/14	Date of Filing Meeting: 4/14/14	
Chemical Classification: (1,2,3 etc.) (original NDAs only) - 3		
Proposed indication(s)/Proposed change(s): Potassium Chloride is indicated for the treatment of patients with hypokalemia with or without metabolic alkalosis, (b) (4)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		
Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic	

	<input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
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<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): P-IND 115294				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Review priority = S
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, explain in comment column.</i>			X	
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>	<input type="checkbox"/>	<input type="checkbox"/>	X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

User Fee Status <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application: <input type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input checked="" type="checkbox"/> Waived (small business waiver granted) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i>					
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</i>					
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code		Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
Exclusivity		YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</i>		<input type="checkbox"/>	<input checked="" type="checkbox"/>		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p>For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?</p> <p><i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i></p> <p><i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

guidance? ¹ If not, explain (e.g., waiver granted).				
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		No clinical trials conducted.

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		No clinical trials conducted.
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment

PREA Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		(the sponsor claimed that this application does not trigger PREA)
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Immediate container labels			
	<input type="checkbox"/> Diluent			
	<input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 6/12/12	<input checked="" type="checkbox"/>	<input type="checkbox"/>		P-IND mtg was essentially a P-NDA mtg.
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE:

BLA/NDA/Supp #: 206814

PROPRIETARY NAME: N/A

ESTABLISHED/PROPER NAME: potassium chloride

DOSAGE FORM/STRENGTH: oral solution 20 mEq/15mL and 40 mEq/15 mL

APPLICANT: Pharma-Med, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Potassium Chloride is indicated for the treatment of patients with hypokalemia with or without metabolic alkalosis, (b) (4)

BACKGROUND: Potassium chloride is approved in various oral tablet formulations but there is no approved oral solution formulation (several manufacturers currently market potassium chloride oral solutions).

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Russell Fortney	Y
	CPMS/TL:	Edward Fromm	
Cross-Discipline Team Leader (CDTL)	Kasturi Srinivasachar		N
Clinical	Reviewer:	Melanie Blank	
	TL:	Martin Rose	
Clinical Microbiology (for antimicrobial products)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Sreedharan Sabarinath	Y
	TL:	Raj Madabushi	N
Biopharmaceutics	Reviewer:	Sandra Suarez	Y
	TL:	Angelica Dorantes	N
Product Quality (CMC)	Reviewer:	Mohan Sapru	N
	TL:	Kasturi Srinivasachar	N
Quality Microbiology	Reviewer:	Denise Miller	N
	TL:	Bryan Riley	N
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Vibhakar Shah	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Jean Olumba	Y
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Other reviewers		
Other attendees	Colleen Locicero Karen Bengston Norman Stockbridge	

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies): The sponsor requested a waiver of BA/BE studies as sotolol tablets are 90-100% bioavailable and the solution is expected to have similar characteristics. While it is not known at the time of filing that the waiver will be granted, it is scientifically plausible and thus the lack of a “bridge” will not prevent filing.</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments: electronic submission is in order.</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: This is an alternate formulation for a drug that has been approved for many years.
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>MICROBIOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL</p>	<input checked="" type="checkbox"/> Not Applicable

<p>(PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<p><input type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: Include request for methods validation in 74-day letter.</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments: At the time of the filing meeting 2 of the 3 manufacturing facilities have an acceptable status. The third facility (Lehigh Valley Technologies) has been assigned for inspection but not yet scheduled.</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Division (Norman Stockbridge)	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL FORTNEY
04/18/2014

Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre- Marketing Applications (Original)

- I. Review Cover Sheet
- II. Application Detail
- III. Filing Checklist
- IV. Manufacturing Summary
- V. Overall Conclusions and Recommendations

I. Review Cover Sheet

1. OMPQ Reviewer: Vibhakar Shah, Ph.D.
2. NDA/BLA Number: 206814
Submission Date: 02/27/2014
21st C. Review Goal Date: 10/26/2014
PDUFA Goal Date: 12/27/2014

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	None
Established or Non-Proprietary Name (USAN) and strength:	Potassium Chloride
Dosage Form:	Oral Solution

4. SUBMISSION PROPERTIES:

Review Priority :	Original STANDARD [505(b)(2)]
Applicant Name:	Pharma-Med, Inc.
Responsible Organization (OND Division):	Division of Cardio-Renal Drug Products

II. Application Detail

1. INDICATION: For the Treatment of hypokalemia, with or without metabolic alkalosis; ^{(b) (4)}

2. ROUTE OF ADMINISTRATION: Oral
3. STRENGTH/POTENCY: 20 mEq/15 mL; 40 mEq/15 mL
4. Rx/OTC DISPENSED: Rx OTC
5. ELECTRONIC SUBMISSION (yes/no)? Yes No
6. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V		X		
2.	Breakthrough Therapy Designation		X		
3.	Orphan Drug Designation		X		
4.	Unapproved New Drug		X		
5.	Medically Necessary Determination		X		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		X		Not applicable/relevant at this stage.
7.	Rolling Submission		X		
8.	Drug/device combination product with consult		X		
9.	Complex manufacturing		X		
10.	Other (e.g., expedited for an unlisted reason)		X		

III. FILING CHECKLIST

The following parameters are necessary in order to initiate a full review (i.e., the application is complete enough to start review but may have deficiencies). On **initial** review of the NDA application:

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	Yes	No	Comment
11.	Is a single comprehensive list of all involved facilities available in one location in the application?	X		
12.	Is all site information complete (e.g., contact information, responsibilities, address)?	X		
13.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	X		
14.	Do all sites indicate they are ready to be inspected (on 356h)?	X		
15.	Additional notes (non-filing issue)	X		
	1. Are all sites registered or have FEI #?			
	2. Do comments in EES indicate a request to participate on inspection(s)?		X	
	3. Is this first application by the applicant?	X	-	DAARTS shows no other application submitted to the Agency by this applicant

*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQ. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
16.	Have any Comparability Protocols been requested?		X	

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

IMA CONCLUSION				
	Parameter	Yes	No	Comment
17.	Does this application fit one of the EES Product Specific Categories?		X	
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion?	X		
	Have all EERs been updated with final PAI recommendation?		X	Not relevant at this stage, i.e., NDA filing stage
19.	<p>From a CGMP/facilities perspective, is the application fileable?</p> <p>If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.</p>	X		

IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements?			
Nanotechnology <input type="checkbox"/>	RTRT Proposal <input type="checkbox"/>	PAT <input type="checkbox"/>	Drug/Device Combo <input checked="" type="checkbox"/>
PET <input type="checkbox"/>	Design Space <input type="checkbox"/>	Continuous Mfg <input type="checkbox"/>	Naturally derived API <input type="checkbox"/>
Other (explain):			

Manufacturing Highlights:

1. Drug Substance

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	Drug substance information in DMF (b) (4) has been previously reviewed and found to be adequate

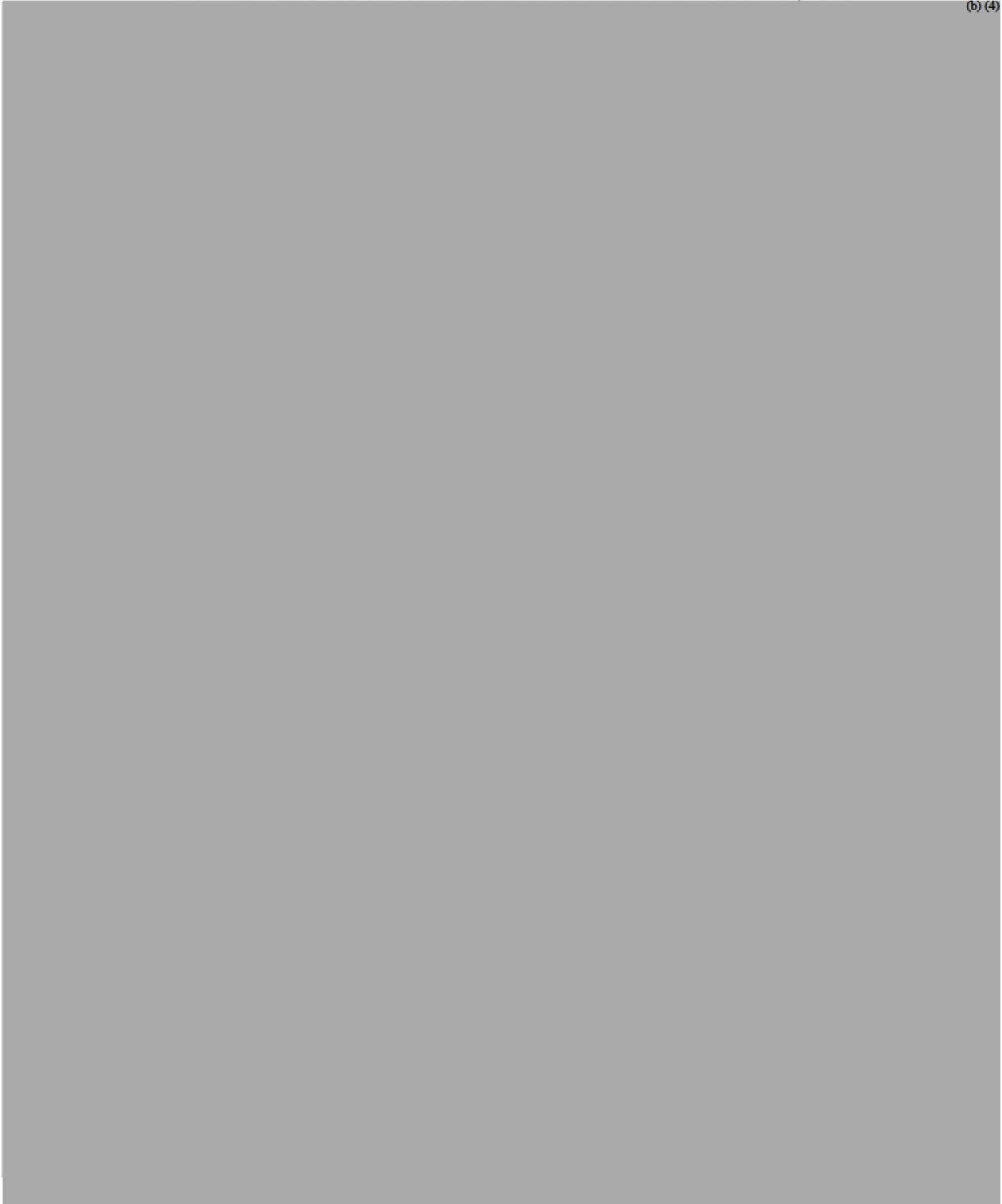
2. Drug Product

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	(b) (4) formulation and manufacturing process

Refer to the drug product manufacturing process flow chart on the page 6.

Drug Product Process Flow Chart/Diagram:

Figure 3.2.P.3.3:F1
Process Flow Chart of Potassium Chloride Oral Solution, USP



3. Facility-Related Risks or Complexities (e.g., number of foreign sites, large number of sites involved, etc.): The facilities listed for the manufacture of the DS as well as the DP are all domestic. Refer to manufacturing facility inspection status update chart on page 8.

Additional information on Manufacturing issues or Complexities

Drug Substance: None noteworthy.

Drug Product: None noteworthy.

Drug substance and Drug Product Manufacturing Facilities Inspection Status Chart

(generated from 602A DARRTS report and OMPQ macro)

Establishment Name	FEI Num	District Short	Country Code	Responsibilities	Profile Code	Inspection History, Dates, Classifications	Facts Assignment ID	Inspection Start -End Date	OAI Alert Status	Most Recent Milestone	Most Recent EER Compliance Status	Comment
(b)(4)	(b)(4)	(b)(4)	USA	(b)(4)	(b)(4)	(b)(4) 05/24/2013]	-	-	-	OC Recommendation 01-APR-2014	AC	DMF (b)(4) Based on Profile EER Re-Eval Date: 23-May-2016
(b)(4)	(b)(4)	(b)(4)	USA	(b)(4)	(b)(4)	(b)(4) 07/23/2012]	-	-	-	OC Recommendation 01-APR-2014	AC	Based on Profile EER Re-Eval Date: 23-JUL-2015
Lehigh Valley Technologies, Inc.	3003851100	PHI	USA	DP Manufacture, package, label, Release and stability Testing	(b)(4)	(b)(4) 12/05/2012]	9329460	TBD	-	Assigned Inspection to IB (b)(4)	PN	Product Specific and GMP Inspection

AC: Acceptable; NA: Not Applicable; TBD: To be determined; PN; Pending

V. Overall Conclusions and Recommendations

Is the application fileable? (yes/no)	YES
At this time, is a KTM warranted for any PAI? (yes – site / no):	NO
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? (yes/no):	NO
Comments for 74 Day Letter	None
1.	
2.	
3.	

REVIEW AND APPROVAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VIBHAKAR J SHAH

04/15/2014

Initial Manufacturing Assessment and Facility Inspection Status Review

MAHESH R RAMANADHAM

04/16/2014