CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208019Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Memo to DARRTS

NDA 208019 **Submission Date: July 28, 2015**
SDN 6

Product: Potassium Chloride Powder for Oral Solution, 20 mEq
Applicant: Pharma Research Software Solution
Indication: Treatment and prevention of hypokalemia with and without metabolic alkalosis
Reviewer: Peter Hinderling, MD

The applicant submitted the following additional publications on July 28, 2015, in support of the 505(b)(2) bridging:

1. Rakhit A, Melethil S, Arnold JD, Wagner WE. Kinetics of Potassium Excretion Following Oral Supplements: Evidence of Induced Natriuresis. Pharm Res 1987;4:531-535
2. Arnold J, Jacob JT, Riley B. Bioavailability and Pharmacokinetics of a New, Slow-Release Potassium Chloride Capsule. J Pharm Sci 1980; 69:1416-1418
3. Betlach JC, Arnold JD, Frost RW, Leese PT, Gonzalez MA. Bioavailability and Pharmacokinetics of a New Sustained-Release Potassium Chloride Tablet. Pharm Res 1987;4:409-411
4. Ben-Ishay D, Engelman K. Bioavailability of Potassium from a Slow-Release Tablet. Clin Pharmacol Ther 1973; 14:250-258
5.Tannen RL, Cordano A. Pharmacokinetics and Effects on Fecal Blood Loss of a Controlled Release Potassium Chloride Tablet. J Pharmacol Expl Ther 1978; 204:240-246

These publications have been reviewed previously by the reviewer (DARRTS date: 06/29/2015) and found to support the bridging of the applicant's liquid KCl formulation

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/s/

PETER HINDERLING
08/03/2015

CLINICAL PHARMACOLOGY REVIEW

NDA Number:	**208019**
Submission Type:	**505 (b) (2)**
Applicant Name:	**Pharma Research Software Solution**
Submission Date:	**October, 24, 2014**
Brand Name:	**To be determined**
Generic Name:	**Potassium Chloride Powder for Oral Solution, USP**
Dosage Form:	**Powder**
Dosage Strengths:	**20 mEq**
Proposed Indication:	**Treatment of patients with hypokalemia with and without metabolic alkalosis;** (b) (4) [redacted]
OCP Division:	**DCP1**
OND Division:	**DCRP, HFD 110**
Primary Reviewer:	**Peter Hinderling, MD**
Secondary Reviewer:	**Raj Madabushi, PhD**

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EXECUTIVE SUMMARY

The applicant is seeking approval for Potassium Chloride KCl Powder for Oral Solution, USP, 20 mEq, by a 505 (b) (2) NDA submission. The 505 (b) (2) NDA is based upon the referenced listed drug (RLD) potassium chloride extended release tablet 10 mEq, Klor-Con® [Upsher-Smith Laboratories (NDA 19123)], a (b) (4) based tablet. The submission requests a waiver for a bioavailability/bioequivalence (BA/BE study) and a waiver for the Pediatric Research Equity Act (PREA) requirements. In support of the request for a BA/BE biowaiver the sponsor submitted 5 published studies that compared the bioavailability of solid and liquid formulation containing KCl and data from the Summary Basis of Approval (SBA) for NDA 19123 for Klor-Con® sustained release tablet, the reference listed drug.

The proposed indications for KCl powder for solution in adults and children is to (b) (4) treat patients with hypokalemia with metabolic alkalosis. In support of the pediatric waiver the sponsor submitted (b) (4)

The Clinical Pharmacology Review focused on the submitted publications and the SBA of NDA 19123 (b) (4) for their product. An additional goal of the review was to identify supplemental literature with information on the bioavailability and pharmacokinetics of potassium after administration of solid and liquid formulations containing KCl to healthy subjects. The Reviewer's data analysis used mean data as individual data of the subjects in the different studies were not consistently available.

1.1 Summary of Important Clinical Pharmacology Findings

- Administration of therapeutic doses of potassium does not result in a commensurate increase of the plasma levels. Thus, the traditional exposure measures, AUC and Cmax, are not useful in determining bioavailability and pharmacokinetics of potassium. Instead, the cumulative amounts excreted in urine, the peak excretion rates and the corresponding times, must be used in assessing bioavailability/bioequivalence of preparations containing KCl.

- Potassium, after oral administration of liquid is primarily eliminated by renal excretion (70-90% of the dose). Smaller amounts (10% of the dose) are eliminated by the fecal route. Although the inter-study variability of the cumulative amounts of potassium excreted is greater than the intra-study variability, absolute bioavailability, peak rates and corresponding times of potassium with liquid formulations are fairly consistent among different studies.

- The mean absorption efficiency of potassium with solid formulations relative to liquid formulations containing KCl is similar and ranges between 80 and 120 %.

- Liquid KCl formulations do not show a food effect

- Distribution and elimination of potassium deviate from linear kinetics. In order to obtain accurate estimates for bioavailability/bioequivalence of KCl containing formulations the collection of urine samples should be extended until the amounts of potassium remaining to be excreted are negligible. The collection of total volumes of urine is a pre-condition for obtaining accurate estimates for the rate and extent of absorption of potassium.

- Many extrinsic and intrinsic cofactors impact the disposition of potassium, including the content of potassium and sodium in the diet, food- and caloric intake, hormones (insulin, aldosterone), β_2-agonists, physical activity and posture. Protocols of bioavailability studies must control for these covariates.

Issues

Biowaiver

- The sponsor has not provided persuasive evidence supporting a biowaiver for their product. The five publications submitted reported urinary excreted amounts of total (net + dietary) potassium instead of net potassium after administration of liquid and solid KCl formulations (1-5). Estimating bioavailability based on amounts of total potassium excreted is not appropriate. Only two of the five publications reported also bioavailability based on the amounts of net potassium excreted 24 h and 48 h after administration of potassium chloride products. One of the two publications demonstrated a lower than 80% bioavailability of net potassium with a solid dosage form relative to a solution. It appears that the sponsor has not analyzed the raw data sets reported in the publications and has not differentiated between the amounts excreted in urine of net and total potassium.
- The sponsor has no right to refer to the bioavailability data reported in the SBA of the RLD Klor-Con

Resolution of the Issues

- The identification of additional publications by the Reviewer and the information provided in NDA 208019 allowed determination of the urinary excreted amounts of net potassium for liquid and solid dosage formulations containing KCl. The results show not only consistency of the bioavailability and pharmacokinetics among liquid KCl formulations but also between liquid and solid formulations containing KCl including

Klor-Con allowing bridging of the sponsor's product, KCl powder for Oral solution, USP, 20 mEq, to Klor-Con.

1.2 Recommendations

The Office of Clinical Pharmacology recommends granting a biowaiver for KCl Powder for Oral Solution, USP, 20 mEq.

1.3 Post-marketing Requirements

None

2. QUESTION BASED REVIEW

2.1 General Attributes of the Drug

2.1.1 History of Regulatory Development

Potassium chloride containing formulations

KCl containing products for intravenous infusion and oral administration are approved for marketing in the US. Oral formulations include liquid and solid products. The initial solid preparations with delayed release characteristics were removed from the market in the 1960s because of gastrointestinal toxicity. Later, wax matrix based and microencapsulated formulations as well as coated microcrystal containing preparations with extended release characteristics were introduced.

Regulatory meetings for NDA 208019

A Type B Meeting for P-IND 115294 for KCl Powder for Oral Solution, USP, 20 mEq per 15 mL, was held on May 23, 2012, with the previous sponsor, Lehigh Valley Technologies, Inc. Allentown, PA. At the meeting the Agency stated that if the sponsor chooses the 505 b(2) path a biowaiver for their product is feasible.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

KCl is a (b) (4) of a molecular mass of 74.55 dalton. It is highly soluble in water (360 mg/mL). The formulation is a powder containing 20 mEq KCl which is to be diluted with (b) (4) 4 ounces of cold water before ingestion.

2.1.3 What are the proposed mechanism of action and therapeutic indications?

K^+ is the principal intracellular cation in most tissues. An electro-chemical gradient across the cell membranes characterized by a 30 fold higher intra-cellular than extracellular concentration of K^+ is required for the functioning of the cells in sustaining intracellular tonicity, the

transmission of nerve impulses, the contraction of cardiac, skeletal and smooth muscles, and the maintenance of normal kidney function.
The therapeutic indications for KCl include treatment of adult and pediatric patients with hypokalemia with or without metabolic alkalosis. (b) (4)

(b) (4)

(b) (4)

2.1.4 What are the proposed dosages and routes of administration?
Potassium chloride for oral solution is to be administered orally. The proposed dosages are for

Treatment of hypokalemia
Adults: Initial doses ranging from 40 to 100 mEq/day in 2-5 divided doses; limit doses to 40 mEq per dose. Total daily dose should not exceed 200 mEq.
Pediatric patients aged birth to 16 years old: 2-4 mg/kg/day in divided doses; not to exceed 1 mEq/kg as a single dose or (b) (4) mEq whichever is lower; if deficits are severe or ongoing losses great consider intravenous therapy. Total daily dose should not exceed 100 mEq.

Maintenance or prophylaxis of hypokalemia:
Adults: Typical dose is 20 mEq per day
Pediatric patients aged birth to 16 years old: Typical dose is 1 mEq/kg/day. Do not exceed 3 mEq/kg/day

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and the clinical studies used to support dosing or claims?
The sponsor has not performed any studies in humans. The submission contains 5 supporting publications that report data from randomized, crossover, single dose bioavailability studies of KCl containing oral formulations.

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?
This is a 505 (b)(2) submission. No response endpoints were measured. See Section 2.2.4 for response endpoints.

2.2.3 Are the active moieties in plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?
The active moiety, K^+, was measured in urine, because the increase in the plasma/serum levels is too small to assess the bioavailability and pharmacokinetics of K^+ with formulations containing KCl.

2.2.4 Exposure-Response
2.2.4.1 What are the characteristics of the exposure-response relationships for efficacy?

The exposure response relationship for efficacy for K^+ is not well understood. The efficacy endpoint in patients with hypokalemia is the serum level of K^+, a biomarker. It is assumed that a normal K^+ level indicates a normal extra-/intracellular gradient of K^+. The dose of KCl is titrated against the serum level of K^+. In adults the normal serum level ranges between 3.5 and 5.5 mEq/L. In children the normal range of serum K^+ levels is age dependent.

2.2.4.2 What are the characteristics of the exposure-response relationships for safety?
The serum K^+ is also used as biomarker for safety. Additional biomarkers for safety include the PQ-, QRS- and QT/QTc intervals and the T wave of the ECG (6). A roughly linear dose-response relationship for K^+ is known for the T wave. With increasing levels of K^+ the QT interval becomes shorter, the PQ interval longer and the QRS interval wider. The dose regimen of KCl is adjusted to the degree of hypokalemia. In clinical practice the serum K^+ levels are monitored routinely.

Single oral doses of up to 140 mEq KCl and daily oral doses of up to 500-1000 mEq KCl from dietary sources have reportedly been tolerated (7). Two of three healthy subjects receiving 167.6 mEq of KCl orally experienced paresthesia starting about 60 min after administration and lasting 60-90 min (8).

2.2.4.3 Does this drug prolong QT/QTc Interval?
No QT/QTc study was performed with KCl containing formulations. No evidence for a prolongation of the QT/QTc interval after administration of KCl formulations is available (see section 2.2.4.2)

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known E-R relationship?
Yes. The dose and dose regimen proposed for KCl Powder for Solution is consistent with previous reported experience. The potassium levels are to be monitored.

2.2.5 What are the PK characteristics of the drug?

Facts Relevant for the Kinetics of Potassium
Potassium is the principal intracellular cation of most body tissues (9). Total K^+ in the human body is about 3500 mEq. Of the total pool 98% (3400 mEq) resides intra-cellularly in muscular tissue, liver and red blood cells and 2.0% (80 mEq) is distributed in the extra-cellular space. The gradient is maintained by the activity of the transporter Na^+/K^+ ATP'ase. Because of the magnitude of the gradient, intracellular K^+ constantly leaks out into the extracellular space. By balancing dietary uptake and loss mainly by renal excretion a quasi-steady-state of K^+ is achieved in the body. A normal diet provides between 50 -100 mEq of K^+ daily. In healthy subjects about 90% and 10% of a dose of K^+ is reportedly eliminated by the renal and fecal routes, respectively (10-12).

In humans, K^+ is passively absorbed in the gastrointestinal tract. Potassium is not bound to plasma proteins (13). The renal clearance of K^+ exhibits a circadian rhythm with a peak at

midday which is 2 fold greater than the nadir at midnight (14). Based on findings in animals two transporters were postulated to be involved in mitigating the increase of the plasma levels of K^+ after acute administration of KCl: The transporter Na^+/K^+ATP'ase located in muscle tissue, the major pool, and in the splanchnic bed, when activated, shifts K^+ from the extracellular to the intracellular space and the Na^+-K^+-Cl^- co-transporter located in the distal tubule and collecting duct of the kidney, when activated, modulates the renal clearance of K^+ by shifting from reabsorption to secretion (15-20). The system regulating activation/inactivation of the transporters has not been identified (21). Other covariates that can impact the kinetics of K^+ include physical activity, caloric intake, insulin, aldosterone, $beta_2$ agonists and sodium (12,22,23).

Pharmacokinetics of Potassium

The goal of the review was to examine suitable published data in healthy humans after administration of liquid and solid dosage formulations containing KCl to determine the pharmacokinetics and bioavailability of K^+. A literature search covering the period from 1930 to 2014 was conducted.

Methods

Selection and Acceptance Criteria of Publications Reporting on the Pharmacokinetics of Potassium

Publications were of interest if they reported:

a) the time course of the excretion rate and the excreted cumulative amounts of K^+ in urine, dAe/dt and Ae(t), respectively, after oral or intravenous single dose administration of KCl. Publications were considered that used a randomized cross-over design, included a control period of 2-4 days with intake of a fixed K^+ diet prior to administration of KCl formulations and reported excretion rate- and recovery data of K^+ on control and treatment days. A total of 8 studies in healthy subjects met the acceptance criteria for a) (1,2,24-28). Among these studies, two collected urine samples frequently up to 48 h after administration so that plots of dAe/dt vs time, and amounts remaining to be excreted in urine, Ae(∞)-Ae(t), versus time could be obtained and peak excretion rates, dAe/dtmax, and corresponding times, tmax, determined. From the remainder 6 studies only partial information was obtainable including e.g. recovery of K^+ 24 h after administration, Ae(0-24), and dAe/dtmax and tmax.

b) mid time plasma/serum concentrations and dAe/dt of K^+ after intravenous infusion or oral administration of KCl . Four (4) publications were identified allowing calculations of CLr (12, 14,29,30). They reported mean data from cohorts of 4-14 healthy subjects obtained on control- and treatment days with single dose administration of liquid and solid KCl formulations, during

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Age, renal impairment, heart failure and liver cirrhosis are intrinsic factors that may impact the safety of KCl containing products. The dose selection should start at the lower end in these populations.

2.3.2 Based upon what is known about E-R relationships and their variability, what dosage regimen adjustments are recommended for each group?

2.3.2.1 Elderly

Clinical studies of KCl did not include sufficient numbers of subjects aged ≥65 years to determine whether they respond differently from younger subjects. In general dose selection for elderly patients should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

The drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

2.3.2.2 Pediatric Patients

The language used in the label for NDA 206814 should be used as follows: Treatment of hypokalemia: Pediatric patients aged birth to 16 years old: The initial dose is 2 to 4 mEq/kg/day; do not exceed as a single dose 1mEq/kg 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

Maintenance or prophylaxis: Pediatric patients aged birth to 16 years old: Typical dose is 1 mEq/day. Do not exceed 3 mEq/kg/day

2.3.2.3 Race

No impact reported

2.3.2.4 What pregnancy and lactation use information is there in the label?

Animal reproduction studies have not been conducted with KCl. It is unlikely that KCl supplementation that does not lead to hyperkalemia would have an adverse effect on the fetus or would affect reproductive capacity.

The normal K^+ content of human milk is about13 mEq/L. Since oral K^+ becomes part of the K^+ pool, so long as the body K^+ is not excessive, the contribution of KCl supplementation should have little effect on the level in human milk.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors influence exposure and/or response, and what is the impact of any difference in exposure on efficacy or safety responses?

Co-administered drugs including potassium sparing diuretics, ACE inhibitors, ARBs, and sodium can impact the K^+ plasma/serum levels. Insulin and $beta_2$ agonists are known to redistribute K^+ from the extracellular space to the intra-cellular space.

2.4.2 What are the drug-drug interactions?

Potassium sparing diuretics: Use with K^+-sparing diuretics can produce severe hyperkalemia. Avoid concomitant use.

*Angiotensin- converting enzyme inhibitors: Use with angiotensin converting enzyme (*ACE) inhibitors produces potassium retention by inhibiting aldosterone production. Potassium supplements should be given to patients receiving ACE inhibitors only with close monitoring.

Angiotensin Receptor Blockers

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

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

The transporter Na^+/K^+ATP'ase pushes extracellular K^+ into tissue cells. The Na^+-K^+-Cl^- Co-transporter is responsible for the secretion of K^+ in the distal convoluted tubule and collecting duct of the kidney. Theoretically, inhibitors or inducers of the Na^+-K^+-Cl^- Co-transporter or the Na^+/K^+ ATPase transporter could impact distribution and elimination of K^+, respectively. Digoxin is a mild inhibitor of the Na^+/K^+ ATP'ase. No inducers of the Na^+/K^+ ATP'ase are known at present. Inducers or inhibitors of the Na^+-K^+- Cl^- Co-transporter are not known.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

K^+ is not a substrate of CYP enzymes. K^+ is not metabolized.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

There is no evidence that K^+ is an inhibitor or inducer of CYP enzymes.

2.4.2.4 Is the drug an inhibitor and/or an inducer of Pg-P transport processes?

There is no evidence that K^+ is an inhibitor or inducer of P-gp.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

The Na^+-K^+-Cl^- Co-transporter is responsible for the tubular secretion of potassium. The shift between net reabsorption to net secretion in the renal tubule is critical for the regulation of the homeostasis of K^+.

2.4.2.7 What other co-medications are likely to be administered to the target population?

Digoxin in patients with congestive heart failure, ACE-inhibitors, angiotensin receptor blockers, diuretics, K^+ sparing diuretics in hypertensive patients.

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?
See Section 2.4.2

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?
The toxicity of digoxin (cardiac arrhythmias) in patients with hypokalemia can be reduced by co-administration of KCl. Digoxin is a mild inhibitor of the transporter Na^+/K^+-ATP'ase

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?
No

2.4.2.11 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?
None

2.5 General Biopharmaceutics
2.5.1 Based on the biopharmaceutics classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?
KCl formulations have not been classified definitively using the BCS classification system. However, KCl is highly soluble in water and the absorption efficiency of K^+ with liquid and solid formulations containing KCl is 70- 90%.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation relative to the service formulation used in the adequate and well controlled studies?

The sponsor requests a biowaiver for their product

2.5.6 What is the effect of food on the bioavailability of the drug from the dosage form?
No food interaction is anticipated for K^+ when administered as KCl solution.

2.6 Analytical Section
2.6.1 How are the active moieties identified and measured in the plasma?
K^+ is the active moiety. K^+ is measured by flame-photometry in urine and plasma/serum

2.6.2 Which metabolites have been selected for analysis and why?
K^+ is elemental. There are no metabolites

2.6.3 For all moieties measured, is free, bound, or total measured?
Total K^+ is measured, but K^+ is not plasma bound so that total and free concentrations of K^+ are identical.

2.6.4 What bioanalytical methods are used to assess concentrations?

Flame-photometry was identified by 6 of the 7 published bioavailability studies as the assay method used to measure K^+ in urine and plasma

2.6.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What is the curve fitting technique?

The seven publications used in the data analysis published between 1970 and 1990 used assay procedures that did not meet today's standards (1, 29-33). Only one publication (1) reported coefficients of variation of 13% and 21% for the high and low concentration standards, respectively, assayed in duplicate with the assay of each urine pool. However, the flame photometric Method can be considered a relatively simple assay that has been used routinely for a long time. Therefore, this deficiency is not considered a major issue.

2.6.6 What are the lower and upper limits of quantitation?

None of the publications provided information on the lower and upper limits of quantitation for K^+.

2.6.7 What are the accuracy, precision, and selectivity at these limits?

Only one publication reported that the precision ranges between 13-21%. No information on the accuracy and selectivity of the assay method was provided.

2.6.8 What is the sample stability under conditions used in the study?

None of the publications reported on the sample stability and identified the sample conditions

2.6.9 What is the QC sample plan?

Only one publication used high and low standards in duplicate together with each sample with unknown K^+ concentrations.

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/s/

PETER HINDERLING
06/29/2015

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BIOPHARMACEUTICS REVIEW

Division of Biopharmaceutics
Office of New Drug Product/OPQ

Application No.:	208019	**Reviewer:** Banu Sizanli Zolnik, Ph.D.	
Division:	Division of Cardiovascular and Renal Products		
Applicant:	Pharma Research Software Solution, LLC	**Biopharmaceutics Lead (Acting):** Elsbeth Chikhale, Ph.D.	
Trade Name:	NA	**Biopharmaceutics Branch Chief (Acting):** Angelica Dorantes, Ph.D.	
Generic Name:	Potassium Chloride for Oral Solution, USP, 20 mEq		
Indication:	Indicated for the treatment of patients with hypokalemia, with or without metabolic alkalosis; (b) (4) (b) (4) (b) (4)	**Date Assigned:**	10/30/2015
		Date of Review:	6/24/2015
Dosage form:	Powder for Solution	**Route of Administration:**	Oral
Strength:	20 mEq		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission Dates	Date of informal/Formal Consult	PDUFA Date
Original Submission dated 10/24/2014 Seq. 0001 dated 12/22/2014	NA	8/24/2015
Type of Submission:	505 (b)(2)	
Review Key Points:	The evaluation of the biowaiver request	

SUMMARY OF BIOPHARMACEUTICS FINDINGS:

Submission:

Pharma Research Software Solution, LLC is seeking approval of Potassium Chloride for Oral Solution, USP, 20 mEq for the treatment of patients with hypokalemia, with or without metabolic alkalosis; (b) (4) . This is a 505 (b) (2) application relying on the previous findings for the demonstration of Safety and Efficacy for NDA 19439 potassium chloride extended release tablets, 20 mEq manufactured by Shering.

Pursuant to 21 CFR 320.22 (a), The Applicant has requested a waiver of the requirement for the submission of evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence of the drug product.

Review

The biopharmaceutics review is focused on the evaluation and acceptability of the data supporting the biowaiver request.

Assessment:

Since KCL is a highly soluble and highly permeable drug substance (BCS Class 1), the impact of any formulation differences; such as presence of sweeteners, lubricant or flavor enhancers/agents or absence of antimicrobial preservative, etc. will have none or minimum impact on the drug's bioavailability.

RECOMMENDATION:

The Division of Biopharmaceutics had reviewed NDA 208019 and its amendment submitted on December 22, 2014. The overall information supports the bridging of the proposed drug product and the products used in the published literature and therefore the Applicant's request for a biowaiver for the proposed potassium chloride powder for oral solution, 20 mEq is granted.

From the Biopharmaceutics perspective, NDA 208019 for Potassium Chloride Powder for Oral Solution, 20 mEq is recommended for **APPROVAL**.

Banu S. Zolnik -S
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Banu Sizanli Zolnik, Ph. D.
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BIOPHARMACEUTICS ASSESSMENT

Drug Substance

The below table summarizes the drug substance properties. Potassium Chloride is reported to be a BCS Class 1 (high solubility, high permeability) drug.

Physicochemical Data for Potassium Chloride, USP

Description	White crystalline or colorless solid (General Chemical)
Solubility	Solubility in water is (b) (4) (b) (4) Soluble in glycerol (b) (4), slightly soluble in alcohol, insoluble in ether.
Melting Point	773°C (MSDS – General Chemical)
Partition Coefficient	(b) (4)
Polymorphism	No polymorphs listed (Refer to DMF (b) (4)
pKa	~7
Hygroscopicity	Hygroscopic
Density	1.984 g/cm^3
Refractive Index	(b) (4)

Drug Product

The proposed potassium chloride for oral solution is a light pink to orange powder with a citrus odor packaged in a pouch. The drug product when reconstituted is an orange colored orange flavored liquid. Each pouch contains 20 mEq of potassium and 20 mEq of chloride provided by 1.5 grams potassium chloride. The composition of the proposed drug product and the function of the components are listed below.

Table 2. Comparative composition information of the proposed product

Composition of Potassium Chloride for Oral Solution, USP, 20 mEq

Component	% w/w	mg/pouch	Function
Potassium Chloride, USP	(b) (4)	1500.00	Active
Colloidal Silicon Dioxide, NF			(b) (4)
Sucralose, NF			
Citric Acid Anhydrous, USP			
Natural and Artificial Orange Flavor [1]			
FD&C Yellow #6 [2]			

[1] The qualitative composition and specification has been provided by the DMF holder.
(b) (4) statements of composition/specifications and CFR compliance have been made available to Lehigh Valley Technologies, Inc. and are provided in this NDA (No. (b) (4) Specification and CFR Compliance)

The drug product dosage is adjusted to the individual needs of each patient. The adult dose for the prevention of hypokalemia is typically 20mEq/day. (b) (4) (b) (4) The dose for

infants/children, [redacted] is 1 to 4 mEq/kg/day, delivered in divided doses, but not to exceed 1 to 2 mEq/kg/dose. Maximum dosing should not exceed 3 mEq/kg/day.

During the mid-cycle meeting, the possibility that the amount of sucralose in the formulation could exceed the FDA CFSAN's daily limit was discussed. Sucralose is [redacted] used as drug excipient and is approved as a food additive permitted for human consumption for direct addition to food. In the proposed drug product, the excipient sucralose is [redacted] in one pouch of 20 mEq KCl. Maximum maintenance dose for a [redacted] human is [redacted]. Thus, the maximum sucralose exposure is [redacted].

The Pre-Clinical Pharmacology/Toxicology Reviewer, Dr. Baichun Yang evaluated the overall information supporting the amount of sucralose in the proposed drug product and concluded the following:

> *"Since the appearance and palatability of the tested potassium chloride batch with sucralose amount of [redacted] was acceptable, and CFSAN approved sucralose ADI is 5 mg/kg/day (= 300 mg/day for a 60-kg human), final formulation with sucralose [redacted]/pouch is acceptable from a pharmacology or toxicology perspective."*

For the specific details on this evaluation, please refer to Dr. Yang's Pharm/Tox review dated 04/27/2015in DARRTS.

Reviewer's Comment:
Although the proposed drug product contains [redacted] sucralose per pouch, and the Pharm/Tox Reviewer found [redacted] sucralose per pouch acceptable. During the review team meeting, it was agreed that this difference in the amount of sucralose does not pose any safety concerns.

BIOWAIVER REQUEST:

In this NDA submission, the Applicant is requesting a waiver of the requirement for the submission of evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence of the drug product.

Data Supporting the Biowaiver Request:

To support the biowaiver request, the Applicant refers to the information from the approved NDA 19123 for potassium chloride extended release tablet 10 mEq (*Klor-Con ER tablets, manufactured by Upsher-Smith labs, approved on April 17, 1986*)

Although the Applicant identified Klor-Con extended release tablet as the listed drug product in support of the biowaiver request as per 21 CFR 320.22 (a), the listed drug product is a tablet, which is different dosage form and therefore a biowaiver request based on 21 CFR 320.22 (a) is not applicable. However, based on CFR 320.24 (b)(6), the Applicant can rely on literature information to support the approval of their proposed

product. It is noted that the submitted information from published literature is currently being evaluated by Dr. Peter Hinderling, Clinical Pharmacology Reviewer from the Office of Clinical Pharmacology.

In support of the biowaiver request the Applicant provided a table comparing the formulations of the approved Klor-Con ER tablets and the proposed drug product; however, the Applicant did not provide any information on the composition of the formulations of the drug products used in the published articles. Therefore, the following comments were conveyed to the Applicant in an information request letter dated December 11, 2014.

1. ***Provide a table comparing the formulation (components and composition) of your proposed drug product versus the formulation of each drug product used in the literature references that you are relying on to support the biowaiver request.***

2. ***Provide a justification for any difference between the formulation of the proposed product and the formulations in the literature with respect to concentration, inactive ingredients, pH etc.***

On 12/22/2014 (amendment Seq. 0001), the Applicant responded to the FDA's IR. In their response they state that (b) (4) Solution (*no longer marketed*), potassium chloride oral solution, 10% (20 mEq/15 mL) is the PK reference product been used to support the proposed drug product. The Applicant also state that the (b) (4) Solution was used to support NDA 19439 (*Potassium chloride extended release tablets, 20 mEq and 10 mEq manufactured by Schering, approved on Jun 13, 1986 and currently off the market*).

The provided comparative composition for the formulations of the proposed and reference drug products is presented in Table 2 below.

Table 2. Comparative composition information between the proposed product and (b) (4) (b) (4) solution, 10% (20 mEq/15 mL)

Ingredients	Function	Pharma Research Software Solution, LLC 20 mEq		(b) (4) 10% (20 mEq/15 mL)	
		% w/w	mg/pouch	% w/v	mg/15 mL
Potassium Chloride	API				(b) (4)
(b) (4)	(b) (4				
Sucralose					
Colloidal Silicon Dioxide					
Citric Acid Anhydrous					
Natural and Artificial Orange Flavor					
FD&C Yellow #6					
(b) (4)					

*While a flavoring agent is present in the (b) (4) formulation, the flavor is not known.

In addition to (b) (4), the Applicant identified three other oral solutions (Kaon-CL (b) (4)) used in the studies from the literature references. The next tables compare the composition information for the proposed drug product and the Kaochlor 10% identified in the literature.

Table 3. Comparative composition information between the proposed product and (b) (4) solution, 10% (20 mEq/15 mL)

Ingredients	Function	Pharma Research Software Solution, LLC 20 mEq		(b) (4) 10% (20 mEq/15 mL)	
		% w/w	mg/pouch	% w/v	mg/15 mL
Potassium Chloride	API	(b) (4)			(b) (4)
Sucralose	(b) (4				
Colloidal Silicon Dioxide					
Citric Acid Anhydrous					
Natural and Artificial Orange Flavor					
FD&C Yellow #6					
FD&C Yellow #5					
(b) (4					

(b) (4) are (b) (4) and therefore contain the same ingredients as (b) (4) except for (b) (4)

** While a flavoring agent is present in the (b) (4) formulation, the flavor is not known.

As noted in Tables 2 and 3, there are formulation differences between the proposed drug product and the products identified in the literature; however, since KCL is a highly soluble and highly permeable drug substance (BCS Class 1), the impact of any formulation differences; such as presence of sweeteners, lubricant or flavor enhancers/ agents or absence of antimicrobial preservative, etc. will have none or minimum impact on the bioavailability of the drug. Therefore, the Division of Biopharmaceutics concludes that the recommendations drawn by the OCP review team on the PK published literature should not be affected by the formulation differences of the drug products used in these publications.

It is noted that a similar approach was already used by the Division of Biopharmaceutics for the approval of a biowaiver request under NDA 206-814 for potassium chloride oral solution, 20 mEq/15 mL and 40 mEq/15 mL (*NDA approved on December 22, 2014*). For specific details, please refer to the Biopharmaceutics review by Dr. Sandra S. Sharp dated 10/16/14 in Panorama.

REVIEWER'S OVERALL ASSESSMENT: SATISFACTORY

The Division of Biopharmaceutics had reviewed NDA 208019 and its amendment submitted on December 22, 2014. The overall information supports the bridging of the proposed drug product and the products used in the published literature and therefore the Applicant's request for a biowaiver for the proposed potassium chloride powder for oral

solution is granted.

From the Biopharmaceutics perspective, NDA 208019 for Potassium Chloride Powder for Oral Solution, 20 mEq is recommended for **APPROVAL**