CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208019Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

TO: NDA 208019

FROM: Rao V. Kambhampati, Senior Chemist

SUBJECT: Labeling Revision and Outcomes of Facilities' Inspections

DATE: 8/19/2015

CC: Edward J. Fromm, RPM (DRCP); Mohan Sapru, CMC Lead (ONDP); Wendy Wilson-Lee, Branch Chief (Branch I, DNDP I, ONDP)

Facility Inspections

OPF provided an overall recommendation of acceptable for all facilities listed for Potassium Chloride for Oral Solution NDA# 208019 on 7/16/2015.

Overall Recommendation

The applicant made all the CMC related changes recommended to the container and carton labels and package insert. The Office of Process and Facilities (OPF) issued an Overall Acceptable Recommendation for all the listed manufacturing and testing facilities of the NDA 208019, therefore, from the CMC perspective the NDA# 208019 is recommended for approval.

Rao V. Kambhampati

Rao V. Kambhampati, Ph.D.
Senior Chemist
Branch I, DNDP I, ONDP

PANORAMA

My Work Projects Reporting Requests Timesheet

NDA 208019-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1) » Manufacturing Facility Inspection

Overall Manufacturing Inspection Recommendation

Edit Task | Task Actions

Task Summary Task Details Issues Updates **Inspection Management Form**

Inspection Management Form As of 12:19 PM

Inspection Management Form

NDA 208019-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)

(b) (4)

LEHIGH VALLEY TECHNOLOGIES INC | 3003851100 | POW POWDERS (INCLUDES ORAL AND TOPICAL) | Approve Facility - 2017-07-06

~~LEHIGH VALLEY TECHNOLOGIES INC | 3003851100 |~~ (b) (4) ~~(b) (4) - FACILITY PROFILE CANCELLED~~

Overall Manufacturing Inspection Recommendation

Approve
Withhold

Overall Application Re-evaluation Date
8/24/15

Cancel

Assigned To

Vibhakar Shah

Ruth Moore

Edit Assignment

This was done on
Jul 16, 2015
(22 days ago)

Status
Complete

Requested by
Yvonne Knight

This task is waiting on
2 Tasks

Last Update
Jul 16, 2015

Submitted On
Oct 28, 2014

Reference Number
2704305

NDA# 208019

Potassium Chloride for Oral Solution USP, 20 mEq

Applicant: Pharma Research Software Solution, LLC

Rao V. Kambhampati, Ph.D.

ONDP/DNDP I/Branch I

Quality (CMC) Review

For Division of Cardiovascular and Renal Products (DCRP)

Chemistry Review Data Sheet

1. NDA# **208019**

2. REVIEW #: 1

3. REVIEW DATE: 6/24/2014

4. REVIEWER: Rao V. Kambhampati, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	**Document Date**
None	

6. SUBMISSIONS BEING REVIEWED:

Original 0000 (1)	10/24/14
Amendment 0001 (2)	12/22/14
Amendment 0002 (3)	1/20/15
Amendment 0003 (4)	2/5/15
Amendment 0004 (5)	4/2/15

1. NAME & ADDRESS OF APPLICANT:

Name: Pharma Research Software Solution, LLC
Address: 84 Rotterdam Road North
Southampton, PA 18966
U.S. Agent: Melissa L. Goodhead
11705 Boyette Road, Suite 171
Riverview, FL 33569

2. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Not provided

b) Non-Proprietary Name (USAN): Potassium Chloride for Oral Solution, USP

c) Code Name/#: None

- Chem. Type: 7

- Submission Priority: S

3. LEGAL BASIS FOR SUBMISSION: NDA (21 CFR 314.50), 505 (b)(2)

4. PHARMACOL CATEGORY: Not provided

   Indication: For the treatment and prophylaxis of hypokalemia in patients for whom dietary management with potassium-rich foods or diuretic dose reduction is insufficient.

5. DOSAGE FORM: Powder for Oral Solution

12. STRENGTH/POTENCY: Each pouch contains approximately 1.5 g of KCl supplying 20 mEq of potassium and 20 mEq of chloride.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

    Chemical Names: Potassium Chloride
    Structural Formula: K-Cl
    Molecular Formula: KCl
    Molecular Weight = 74.55

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED
(b) (4)	II		(b) (4)	Adequate	2/26/13 and 7/12/12
	IV			Adequate	Based on information

		(b) (4)		provided in NDA.
(b) (4)	III		Adequate	Based on information provided in NDA.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	019123	Potassium Chloride Extended-Release Tablets, 8 mEq and 10 mEq; approved 4/17/86.
NDA	206814	Potassium Chloride Oral Solution, Applicant: Pharma-Med, Inc., approved.

STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Manufacturing and Testing Facilities	Withhold Approval of Lehigh Valley Technologies drug product manufacturing facility.	6/18/15	Karyn M Campbell, Director, Investigations Branch, Philadelphia District (FDA)
ONDP Biopharm	Review not required for quality because specification doesn't contain dissolution test.	6/24/15	Rao Kambhampati, Ph.D.
LNC (ONDP) for Established Name	Not applicable. USAN name available.	6/24/15	Rao Kambhampati, Ph.D.
Method Validation	Not necessary per current office Policy	6/24/15	Rao Kambhampati, Ph.D.
Package Insert and Medication Guide	Pending by DCRP and others.	6/24/15	Rao Kambhampati, Ph.D.
Container labels and prescribing information	Pending (some changes were recommended)	5/4/2015	Janine A Stewart (DMEPA/OMEPRM/OSE).
Proprietary name	Not applicable	6/24/15	Rao Kambhampati, PhD
EA	Acceptable based on categorical exclusion.	6/24/15	Rao Kambhampati, PhD
Product Quality Microbiology	Microbial limits method acceptable. Review filed in DARRTS.	3/5/15	Erika Pfeiler, Ph.D. (OPF)

The Chemistry Review for NDA 208019

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the Chemistry, Manufacturing, and Controls (CMC) review stand point, the final recommendation for NDA# 208019 for Potassium Chloride for Oral Solution USP, 20 mEq is pending until the following issues are completed:

1. The Lehigh Valley Technologies drug product manufacturing facility is acceptable to the Office of Compliance (OC) and an Overall Acceptable recommendation is issued by the OC for this NDA.

2. The Package Insert and Container and Carton labels are revised and acceptable to all the concerned divisions within the CDER.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance: The drug substance is Potassium Chloride (KCl) and the CMC information was cross-referenced the DMF (b) (4), which was previously reviewed and found to be adequate.

Drug Product: The drug product is Potassium Chloride for Oral Solution, USP, 20 mEq. It is a light pink to orange powder (b) (4) in a pouch. When the drug product is reconstituted in water, it will form an orange colored, orange flavored liquid. The fill weight of each pouch is approximately (b) (4) which will provide a minimum dose of 1.5 grams, which will provide 20 mEq of potassium and 20 mEq of chloride. The components include Potassium Chloride USP; colloidal silicon dioxide NF (lubricant); sucralose NF (b) (4); citric acid anhydrous USP (b) (4) Natural and Artificial Orange Flavor, and FD&C Yellow #6. The qualitative composition and specification for the Orange flavor and FD&C Yellow #6 were provided by the DMF Holders and they are acceptable. The proposed components and their levels in the drug product formulation were derived by performing appropriate process developmental

studies. Compatibility of Potassium Chloride with the excipients and the proposed pouch is demonstrated by conducting stability studies. The proposed specification for the drug product included Description (light pink to orange powder), Identification A for potassium and Identification B for Chloride as according to USP monograph; Assay (NLT [redacted]); [redacted] Uniformity of Dosage Units (USP <905>); Container/Closure System; and Microbial Limits (USP <61> and <62>). Adequate description was provided for non-compendial tests and justification was provided for all the tests and acceptance criteria. The microbial limits test was added upon comment. The proposed tests and their acceptance criteria are acceptable. Batch analysis results were provided for three NDA registration product scale lots and it was demonstrated that the manufacturing process produces lots with consistent quality and purity. The assay values ranged from [redacted] and the [redacted] CoAs were provided for all three lots and they are acceptable. Levels were proposed for potential non-process impurities and they are the same as those proposed for the drug [redacted]. No new impurities were found either at the time of lot release or during stability studies. Complete description was provided for the pouch that is used for packaging of the drug product powder. Qualification studies were conducted on the pouch and the container permeation testing results are acceptable. The updated stability data included 12 months of long-term and 6 months of accelerated data for three NDA registration lots that were manufactured at the full production scale. The results of all three batches were within the proposed stability specification and no new impurities were found. Regression analysis was performed which indicated that all lots are stable for a period of at least 24 months. Based on the real time 12 months long-term stability data and regression analysis, the applicant requested an expiration dating period of 24 months when the drug product is stored at 25°C, which is acceptable.

B. Description of How the Drug Product is Intended to be Used

The drug product is indicated for the treatment and prophylaxis of hypokalemia with or without metabolic alkalosis, in patients for whom dietary management with potassium-rich foods or diuretic dose reduction is insufficient. The drug product powder is reconstituted in water prior to administration to patients. For adults, the initial dose range is from 40-100 mEq/day in 2 to 5 divided doses with a limit of 40 mEq per dose. The total daily dose should not exceed 200 mEq. For pediatric patients aged birth to 16 years old, 2-4 mEq/kg/day in divided doses; not to exceed 1 mEq/kg as a single dose or [redacted] mEq whichever is lower and the total daily dose should not exceed 100 mEq.

Each pouch contains approximately [redacted] of the drug product powder, which will provide a minimum of 1.5 g for dosing, which is equivalent 20 mEq of potassium and 20 mEq of chloride. Pouches are packaged in secondary cartons containing 30 or 100 pouches per carton. The drug product is stored at USP Controlled Room Temperature, 25°C (77°F); excursions are permitted to 15°C-30°C (59°F-86°F).

C. Basis for Approvability or Not-Approval Recommendation

The applicant proposed to use the same drug substance manufacturer that is currently approved under the NDA# 206814 and the CMC information is essentially same as the one described in the DMF# (b) (4), which is currently adequate. The proposed components and composition of the drug product, manufacturing and packaging process, specification, container and closure system, and stability data are acceptable. From the product microbiology stand point, the reviewer recommended approval. The ONDP Biopharm review is not required for quality because there is no dissolution test in the drug product specification. The drug substance facility is acceptable on the basis of profile. The drug product manufacturing facility is on withhold (b) (4) The package insert, container and carton labels are in the process of revision. The final product quality recommendation is pending because of the pending final labeling revisions and an acceptable recommendation for the drug product manufacturing facility.

III. Administrative

A. Reviewer's Signature
Rao V. Kambhampati, Ph.D.

B. Endorsement Block

Primary Reviewer: Rao V. Kambhampati, Ph.D.
Senior Chemist/ONDP/DNDP I/Branch I

Secondary Reviewer: Wendy Wilson-Lee, Ph.D.
Acting Branch Chief/ONDP/DNDP I/Branch I

Digitally signed by Rao V. Kambhampati -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300073803, cn=Rao V. Kambhampati -A
Date: 2015.06.25 10:48:30 -04'00'

Wendy I. Wilson -S
Digitally signed by Wendy I. Wilson -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300396790, cn=Wendy I. Wilson -S
Date: 2015.06.25 10:53:21 -04'00'

Final Quality Assessment of Product Quality Risk:

Initial Quality Assessment			Review Assessment	
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking**	**Risk Evaluation**	**Lifecycle Considerations/Comments**
Appearance	Color fading and agglomeration	L	Acceptable	During developmental and stability studies color fading or agglomeration of particles in powder was not observed. Changes to the formulation and pouch could affect color and may cause agglomeration of particles in powder. Changes to (b) (4)
Assay/stability	Ingredient weights (b) (4) (b) (4)	L	Acceptable	No formation of organic impurities observed during developmental and stability studies. No significant increase in inorganic impurities was observed. Process controls (b) (4) of manufacturing process.
Identification		L	Acceptable	
Uniformity of Dosage Units (Content Uniformity)	(b) (4)		Acceptable	(b) (4)

Water content	[redacted] (b) (4)		Acceptable	[redacted] (b) (4)
Container/Closure system	Changes to the container/closure components	L	Acceptable	Changes to the container/closure system could [redacted] (b) (4) property of the powder.
Microbial limits	[redacted] (b) (4)		Acceptable	Changes to the container and closure system [redacted] (b) (4) acceptance criterion could affect microbial content.

Chemistry Assessment

3.2.S. DRUG SUBSTANCE – Potassium Chloride, USP

Note: The applicant cross referenced the CMC information for Potassium Chloride USP drug substance to the DMF# (b) (4) (Holder: (b) (4)), which was previously reviewed and found to be adequate.

3.2.S.1. General Information

Nomenclature:

International Non-Proprietary Name (INN)	Potassium Chloride
Chemical Name	Potassium Chloride
Chemical Abstract Services (CAS) Registry No.	(b) (4)
Other Names	(b) (4)

Structural Formula: K-Cl
Molecular Formula: KCl
Molecular Weight: 74.55

Comments: Acceptable. The structural formula, molecular formula, and molecular weight were provided as according to USAN.

General Properties:

Description	White crystalline or colorless solid ([(b) (4)])
Solubility	Solubility in water is 281 g/L at 0°C, 344 g/L at 20°C and 567 g/L at 100°C. Soluble in glycerol and alkalies, slightly soluble in alcohol, insoluble in ether.
Melting Point	773°C ([(b) (4)])
Partition Coefficient	[(b) (4)]
Polymorphism	No polymorphs listed ([(b) (4)])
pKa	~7
Hygroscopicity	Hygroscopic
Density	1.984 g/cm^3
Refractive Index	[(b) (4)]

Comments: All expected physic-chemical properties for an inorganic salt were provided.

3.2.S.2. Drug Substance Manufacture
Manufacturer

Facility	FEI/CFN Number	Responsibility
[redacted] (b) (4)		Manufacture, release and stability testing
Lehigh Valley Technologies, Inc. 514 N. 12th Street Allentown, PA 18102 Contact: William Reightler VP of Regulatory Affairs Phone: (610) 782-9780 ext. 18 Fax: (610) 782-9781	3003851100	Acceptance testing

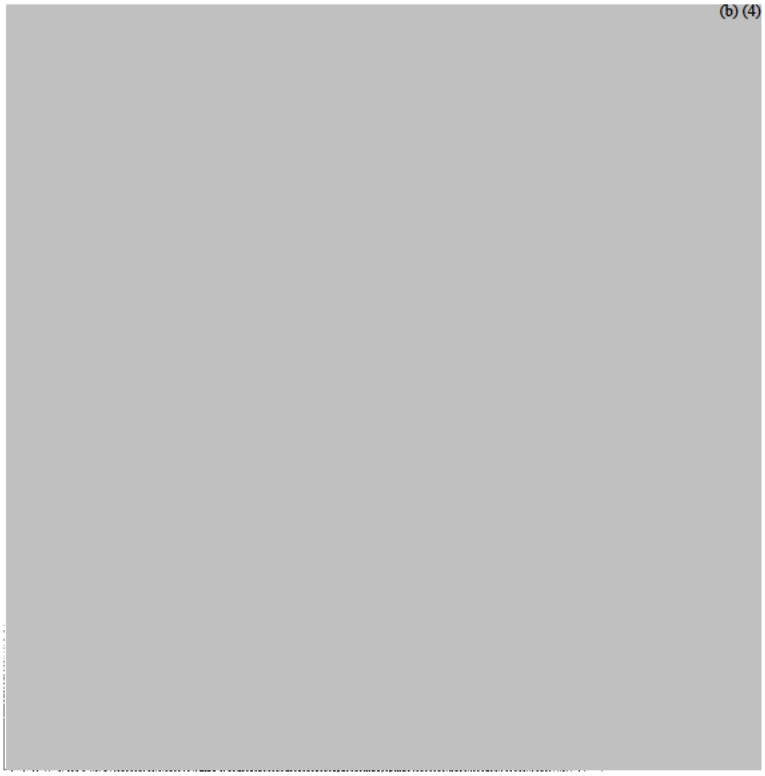
Comments: Acceptable. The applicant provided complete address and contact information for the drug substance manufacturing and testing sites including the facility establishment numbers. A LOA for the cross-reference of the CMC information in the DMF# (b) (4) ((b) (4)) was also provided in the NDA, which was reviewed recently by the chemistry reviewer (ONDP) and it is adequate and the DMF review was filed in DARRTS.

The following subsections were cross-referenced to the DMF# (b) (4)
Manufacturing Process and Process Controls
Control of Materials
Control of Critical Steps
Process Validation and/or Evaluation
Manufacturing Process Development

3.2.S.3. Characterization

Known non-process impurities of potassium chloride, USP are provided in the following table:

Table 3.2.S.3.2:T1
Potential Non-Process Impurities in Potassium Chloride, USP



Comments: Acceptable. The applicant is monitoring all the likely non-process impurities in the drug substance.

3.2.S.4. Control of Drug Substance:
Drug Substance Specification:

The initial submission contained the following specification table:

Test	Specification	Method
(b) (4)		

[1] Required for extension of release.
[2] Required for reduced testing.

Upon review of the above proposed specification, in the IR letter dated 3/26/15, the following comments were communicated to the applicant and the applicant responded in the amendment dated 4/2/15.

With regard to the Proposed Regulatory Drug Substance Specification for Potassium Chloride (Table 3.2.S.4.1:T1), please clarify the following:

(b) (4)

25 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Comments: The methods were shown to be accurate and precise.

Environmental Assessment:

The applicant requested categorical exclusion (21 CFR 25.31 (a) from EA assessment requirement and also stated that the drug product to be manufactured will not increase the use of the active moiety because potassium chloride is currently marketed as a single ingredient and approval of this NDA will result in the replacement of of the use of unapproved versions of potassium chloride products currently in the market. The applicant also stated that Pharma Research Sofware Solution, LLC is also in full compliance with applicable local, state, and federal environmental rules and regulations. The applicant stated that the proposed action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

Comments: The applicant's request for categorical exclusion from environmental assessment requirement is acceptable.

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert:

Labeling:

Copies of the initially submitted pouch and carton labels are provided below:

Proposed Container (Pouch) Label (front):

DMEPA recommended the following changes in their review:

Container Labels:

1. As currently presented, the manufacturer's information is more prominent than the established name due to the blue font utilized in its presentation. Revise the font color of the manufacture information to black or relocate this information to the bottom of the principal display panel (PDP).
2. Remove the "(b) (4) "statement from the PDP. This information contributes to clutter on the PDP and is redundant since it appears on the back panel of the container label.
3. The net quantity per pouch noted on the pouch label (b) (4) is inconsistent with the net quantity noted on the carton labeling, and the Prescribing Information (1.5 g). Ensure that the net quantity is consistent between all labels and labeling.
4. Revise the (b) (4)" statement on the back panel to read "Usual Dose: See prescribing information."

Carton Labels:

1. Revise the net quantity statement (b) (4) to 100 Single-Dose Pouches.

2. If space permitted, add the statement "Dissolve the contents of 1 pouch in 4 ounces of water or other beverages" to the PDP.

Comments: Pending. This reviewer agrees with the DMEPA recommendations.

Package Insert: The initial submission contained the following CMC related information:

3 DOSAGE FORMS AND STRENGTHS

Each pouch contains 1.5 g of potassium chloride supplying 20 mEq of potassium and 20 mEq of chloride.

11 DESCRIPTION

Potassium Chloride is a white crystalline or colorless solid. It is soluble in water and slightly soluble in alcohol. Chemically, Potassium Chloride is K-Cl with a molecular mass of 74.55.

(b) (4) Each pouch of light pink to orange powder contains 1.5 g of potassium chloride, USP and the following inactive ingredients: citric acid anhydrous, colloidal silicon dioxide, FD&C Yellow #6, natural/artificial orange flavor, sucralose.

16 HOW SUPPLIED/STORAGE AND HANDLING

Potassium Chloride for Oral Solution, is a light pink to orange powder available in one strength as follows:

20 mEq:
NDC# 64950-321-20 pouch. Each pouch contains 1.5 g of potassium chloride providing potassium 20 mEq and chloride 20 mEq

NDC# 64950-321-30 carton of 30 pouches
NDC# 64950-321-01 carton of 100 pouches

Storage
Store at Controlled Room Temperature, 25°C (77°F); excursions are permitted to 15°-30°C (59°-86°F).
Dispense in a tight, light-resistant container as defined in the USP
PROTECT from LIGHT.

Comments: Pending. The actual content of each pouch is approximately (b) (4) *which will allow a minimum dosage of 1.5 g of the powder. The applicant needs to state this in all the relevant sections of the package insert.*

III. List of Outstanding Deficiencies: None