

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206814Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service, Food and Drug Administration
Center for Drug Evaluation and Research

DATE: December 9, 2014

TO: File

THROUGH: Olen Stephens, Ph.D., Acting Branch Chief, ONDQA

FROM: Mohan K. Sapru, Ph.D., Senior CMC Reviewer

SUBJECT: Final CMC Approval Recommendation for NDA 206814 (Potassium Chloride Oral Solution)

Background: The applicant, Pharma-Med, Inc., has sought U.S. marketing approval for Potassium Chloride Oral Solution under the provisions of Section 505(b)(2) of the Federal Food and Cosmetic Act and 21 CFR §314.54. Based on the Chemistry, Manufacturing and Controls (CMC) review for this NDA (refer to Quality Review in Panorama by Dr. Mohan Sapru, dated 11/29/2014); there were no pending CMC deficiencies. However, from the CMC perspective, the NDA 206814 could not be recommended for approval because the Office of Compliance had not issued an overall ‘acceptable’ recommendation for the relevant manufacturing and testing facilities.

Update: Based on the ‘Overall Manufacturing Inspection Recommendation’ (entered in Panorama on 12/09/2014), the Office of Compliance has revised the assessment of the facilities, and has made an overall “acceptable” recommendation for all the listed manufacturing and testing facilities (refer to ‘Overall Manufacturing Inspection Recommendation’ at the end of this memo).

Recommendation and Conclusion on Approvability: In view of the overall “acceptable” recommendation by the Office of Compliance for all the listed manufacturing and testing facilities, from the CMC perspective, the new drug application (NDA 206814) for Potassium Chloride Oral Solution is recommended for approval.

The screenshot shows the Panorama software interface. At the top, there is a navigation bar with 'My', 'Find', 'Create', 'Recent', and 'Favorites' menus, along with a search box and a 'Help' button. Below the navigation bar, the breadcrumb trail reads 'Reports > Report > Project > Parent Task > Task'. The user's name 'Mohan Sapru' is visible in the top right corner. The main content area displays the task title 'Overall Manufacturing Inspection Recommendation' with a 'Next task >' link. Below the title, there are tabs for 'Task Details', 'Task Data', 'Open Issues', and 'More'. The 'Task Data' tab is active, showing the task name 'Facility Inspection - Overall Application Recommendation' and the action 'Approve'. Below this, another task is listed: 'Facility Inspection - Overall Application Re-evaluation Date' with a date of '7/23/15'. On the left side, there is a sidebar menu with options like 'View Task', 'Edit Task', 'Copy Task', 'Move Task', 'New Task', 'View Open Issues', 'View All Issues', 'New Issue', 'View SubTasks', 'New SubTask', 'Reports', 'View Hours', 'View Parent Task', 'View Project', 'Attachments', and 'Import/Export'.

Olen Stephens -S
Digitally signed by Olen Stephens -S
DN: cn=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Olen
Stephens -S, 0.9.2342.19200300.100.1.1=2000558826
Date: 2014.12.09 11:56:41 -0500



NDA 206814 (Potassium Chloride Oral Solution)

Pharma-Med, Inc.

Mohan K. Sapru, Ph.D.

*Office of New Drug Quality Assessment
Division I/Branch I*

*Reviewed for the Division of Cardiovascular and Renal Products,
HFD-110.*



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CHEMISTRY REVIEW



1. NDA: 206814 (Potassium Chloride Oral Solution)
2. REVIEW #: 1
3. REVIEW COMPLETION DATE: October 25, 2014
4. REVIEWER: Mohan K. Sapru, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
N/A	N/A

6. SUBMISSION(S) REVIEWED:

Submission (s) Reviewed	Document Date
<u>Original Submission</u>	February 27 , 2014
Applicant's CMC Response Submission (Seq 0003)	June 30, 2014
Applicant's CMC Amendment (SN004)	September 23, 2014
Applicant's CMC Amendment (SN005)	October 21, 2014

7. NAME OF APPLICANT: Pharma-Med, Incorporated.

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: To be decided
- b) Non-Proprietary Name (USAN): Potassium chloride oral solution, USP
- c) Code Name/ # (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):



- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: The application was submitted under Section 505(b)(2) of the Federal Food Drug and Cosmetic Act and 21 CFR §314.54

Potassium chloride is indicated for the treatment of patients with hypokalemia with or without metabolic alkalosis, (b) (4)



11. DOSAGE FORM: Solution
12. STRENGTH/POTENCY: 20 mEq/15 mL or 40 mEq/15 mL
- ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS Product – Form Completed.

Not a SPOTS Product.

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

Chemical Name: Potassium Chloride

Molecular Formula: KCl

Relative Molecular Mass: 74.55

CAS No.: 7447407

17 RELATED/SUPPORTING DOCUMENTS:

A. DMF(s):

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ₂	DATE REVIEW COMPLETED
(b) (4)	II	(b) (4)	Potassium chloride, USP drug substance	3	Adequate	July 12, 2012

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

- Type 1 DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

Letter of authorization (LOA): LOA to DMF #5440 has been provided.

18. STATUS:

ONDQA: (Next Page)



CHEMISTRY REVIEW



CONSULTS/ CMC-RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending	October 25, 2014	
Methods Validation	Not requested. The methods are conventional and don't qualify for internal validation by the FDA laboratories	September 30, 2014	Mohan K. Sapru, Ph.D.
Environmental Assessment	Categorical Exclusion	September 30, 2014	Mohan K. Sapru, Ph.D.
Biopharmaceutics	Recommends approval	October 21, 2014	Sandra Suarez, Ph.D.
Microbiology	Recommends approval	October 23, 2014	Denise Miller, Ph.D.

The Executive Summary (NDA 206814)

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls (CMC) perspective, this new drug application # 206814 for potassium chloride will be recommended for approval provided the Office of Compliance issues an overall 'acceptable' recommendation for the manufacturing facilities. A follow up memorandum, which specifies the final CMC recommendation, will be submitted after the recommendation from the Office of Compliance is finalized.

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

Not applicable at this stage.

II. Summary of Chemistry Assessments

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

Drug Substance: Potassium chloride is a (b) (4) (b) (4) For details concerning the drug substance such as structural characterization, manufacturing process, control of materials, control of critical steps, process validation, manufacturing process development, container closure system, and stability, the applicant has referred to Type II DMF (b) (4) which has been last reviewed on July 12, 2012 and found to be adequate. The applicant has indicated that there are no organic process impurities of potassium chloride. The levels of non-process impurities in the drug substance manufactured by (b) (4) have been provided and are acceptable. From quality risk assessment point-of-view, it is important to note that (b) (4) levels are controlled by drug substance specification. The proposed retest period is supported by drug substance stability data provided in the DMF (b) (4) which has previously found to be adequate. Based on the proposed control strategy, the critical quality attributes of an (b) (4) drug substance are controlled largely by appropriate specification.

Drug Product: The proposed drug product i.e., potassium chloride (KCl) oral solution, USP, 20 mEq/15 mL or 40 mEq/15 mL is a clear orange-colored, orange-flavored oral solution, which is packaged in a (b) (4) white high density polyethylene (HDPE) bottle with a (b) (4). The proposed drug product is formulated to be (b) (4). Potassium chloride oral solution is not listed in the 'Orange Book'. Several unapproved versions of the product are available commercially. The product has a USP monograph. The proposed control strategy to ensure product quality is adequate. To ensure that the drug substance meets all specifications, batches of drug substance (used in the drug product formulation) are retested at (b) (4) the drug product manufacturer. Although not an oral solution, potassium chloride extended release tablet, 20 mEq from Schering-Plough Corporation (NDA 019439), has been used as the reference listed drug (RLD). Based on formulation development studies, the dosage form proposed has been optimized to provide the drug product with the desired attributes relevant to flavor selection, colorant selection, and preservative effectiveness against microbial contamination. The straightforward manufacturing process involves

The Executive Summary (Continued)

the typical steps commonly used for this type of dosage form and has been validated. The process controls entail the monitoring and recording of mixing speeds, mixing times, and ingredient weights at every step during the manufacturing process. No excipients of human or animal origin are used in the manufacture of the drug product. The compendial excipients are controlled based on the USP monographs. All compendial excipients suppliers have provided BSE/TSE statements.

The drug product specification appropriately includes testing for critical quality attributes i.e., appearance, identification, 'assay', preservative content, and microbial limits. Together, data from validation studies demonstrate that the listed analytical methods, including the HPLC method used for determination of preservatives methylparaben and propylparaben in potassium chloride oral solution are suitable for intended application. Since potassium chloride oral solution will be commercially distributed in a packaging configuration for repeated use, preservatives methylparaben and propylparaben are used in the formulation at the concentrations of (b) (4). These concentrations fall within the range tested for antimicrobial effectiveness and are commonly used in the currently marketed oral liquid products. Together, data from validation studies demonstrate that the listed analytical methods, including the HPLC method used for determination of methylparaben and propylparaben in potassium chloride oral solution, are suitable for intended application.

Based on literature findings, the preservatives such as methylparaben are known to retain activity over a wide pH range of (b) (4). However, during preapproval inspection of the drug product manufacturing facility, the field investigator discovered that there are significant variations in the drug product pH on storage. Hence, the applicant's proposal to (b) (4) has not been accepted. To ensure batch-batch consistency in the effectiveness of the preservatives methylparaben and propylparaben, the applicant has revised drug product specification by including a test for monitoring drug product pH (acceptance limit for pH in the range of (b) (4)). The drug product stability studies are ongoing. Stability data provided indicate that drug product is stable for 12 months at 25 °C / 60% relative humidity (RH) or for 6 months at 40°C / 75% RH. No trends in any of the stability parameters that are being monitored have been observed. Regarding applicant's post-approval commitment, the first three commercial scale batches will be placed on long-term ICH stability study, and a representative manufacturing batch will be monitored on long-term stability annually. The applicant has committed to submit stability summaries and stability testing results to the Agency annually in accordance with 21 CFR 314.81(b)(2)(iv)(a).

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

The proposed drug product i.e., potassium chloride (KCl) oral solution, USP, 20 mEq/15 mL or 40 mEq/15 mL will be packaged in a (b) (4) mL white high density polyethylene bottle (b) (4). Potassium chloride oral solution is indicated for the treatment of patients with hypokalemia with or without metabolic alkalosis, (b) (4).

The content of the oral solution is to be diluted with at least 4 ounces of cold water. This preparation, like all potassium supplements, needs to be properly diluted to avoid the possibility of gastrointestinal irritation and is recommended to be taken with meals or immediately after eating. The stability data support a 24-month expiry period for the drug product when stored at room temperature (15° - 30°C; 59° - 86°F) using the applicant's proposed container/closure system.

The Executive Summary (Continued)

C. Risk Assessment. Risk assessment summary is tabulated below.

Initial Risk Assessment

Product Attribute/CQA	Factors that Can Impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number*	Comment
Assay, stability	Impurity formation exceeds specification				(b) (4)	
Physical stability (phase separation)	Phase separation				(b) (4)	
Physical stability (solid state)	(b) (4)h (b) (4) (b) (4)				(b) (4)	
Dosing accuracy	Inaccurate dosing due to changes in homogeneity, droplet size distribution, rheology				(b) (4)	
Palatability	Failure to mask unpleasant taste/smell				(b) (4)	
Microbial limits	Presence of microbes				(b) (4)	
Leachables	Generation of impurities				(b) (4)	

* RPN ≤ 25: Low risk

* RPN > 25 and ≤ 60: Moderate Risk;

* RPN > 60: High Risk

The Executive Summary (Continued)

Final Risk Assessment

Product Attribute/ CQA	Factors that Can Impact the CQA	FMECA RPN Number	Final Risk Assessment	Mitigation of Risks	Comments for Post- Marketing Considerations
Assay, stability	Impurity formation exceeds specification	(b) (4)	Acceptable Risk	Drug substance (DS), an inorganic salt, is inherently stable. No organic impurities are present in DS. Quality control strategies, including DS and DP specifications are adequate	Any change in DS or DP manufacturing process or specification would need to be evaluated in the context of overall impact on quality control strategy. Evaluation of post-approval stability data is needed for granting any extension of drug product expiry period
Physical stability (phase separation)	Phase separation	(b) (4)	Acceptable Risk	Physical properties, formulation/ product development and stability studies do not indicate any phase separation	N/A
Physical stability (solid state)	(b) (4) (b) (4)	(b) (4)	Acceptable Risk	(b) (4) (b) (4) (b) (4)	N/A
Dosing accuracy	Inaccurate dosing due to changes in homogeneity, droplet size distribution, rheology	(b) (4)	Acceptable Risk	KCl is a low risk product with wide therapeutic window. Mention of dosing cup, and tablespoonful dispensing is included. Labelling/PI will add further clarity	N/A
Palatability	Failure to mask unpleasant taste/smell	(b) (4)	Acceptable Risk	Formulation contains glycerin, sucralose and flavor	N/A
Microbial limits	Presence of microbes	(b) (4)	Acceptable Risk	Preservatives prevent microbial growth. Their effectiveness is controlled by specification for preservative content and drug product pH	Any changes in preservative system need to be evaluated in the context of control strategy, including specification for preservative effectiveness
Leachables	Generation of impurities	(b) (4)	Acceptable Risk	Extractability studies show no evidence of leachables/ impurities	Any significant change in container closure system or sealing materials would need to be evaluated for potential leachables impurities

**The Executive Summary (Continued)****D. Basis for Approvability or Not-Approval Recommendation.**

In essence, review of this application was based on risk-based approach. Based on the review of the original submission, several deficiencies concerning the drug product were identified and communicated to the applicant. These deficiencies mainly concerned inadequate information and/or data provided regarding specifications for the drug substance and the drug product, control strategies, stability data and post-approval commitment for the drug product. The applicant has satisfactorily addressed all the identified deficiencies. Specifically, per amendment SN 005, the sponsor has agreed to revise the proposed drug substance specification to include 'assay' for reduced testing using a validated analytical method. Furthermore, in compliance with the Agency recommendation, the applicant has revised the drug product specification by including a test for monitoring drug product pH with an acceptance limit for pH in the range of 3.0 – 6.5 to ensure preservative effectiveness on storage. The applicant's updated stability data are acceptable and support the proposed 24-month expiry period for the drug product. Regarding the Biopharmaceutics and Microbiology aspects of this application, the concerned reviewers have recommended approval for this NDA.

In summary, based on CMC review of this NDA, there are no pending CMC-related deficiencies. However, at this stage, the Office of Compliance has not issued an overall recommendation for all the manufacturing facilities. In conclusion, from the chemistry, manufacturing and controls (CMC) perspective, this new drug application # 206814 for potassium chloride will be recommended for approval provided the Office of Compliance issues an overall 'acceptable' recommendation for the manufacturing facilities.

Administrative.**A. Reviewer's Signature**

Mohan Sapru

B. Endorsement Block

Review Chemist: Mohan K. Sapru, Ph.D.

Acting Branch Chief: Olen Stephens, Ph.D.

C. CC Block

Project Manager: Alexis, Childers

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: 206814

2. DATES AND GOALS:

Letter Date: Feb. 27, 2014	Submission Received Date : Feb. 27, 2014
PDUFA Goal Date:	Dec. 27, 2014

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	None
Established or Non-Proprietary Name (USAN):	Potassium Chloride
Dosage Form:	Oral solution
Route of Administration	Oral
Strength/Potency	20 mEq per 15 mL and 40 mEq per 15 mL
Rx/OTC Dispensed:	Rx

4. INDICATION: Treatment of hypokalemia, with or without metabolic alkalosis; (b) (4)

5. DRUG SUBSTANCE STRUCTURAL FORMULA:

KCl

6. NAME OF APPLICANT (as indicated on Form 356h):

Pharma-Med, Inc.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

7. SUBMISSION PROPERTIES:

Review Priority:	Standard
Submission Classification (Chemical Classification Code):	Type 3
Application Type:	505(b)(2)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	Division of Cardiovascular and Renal Products

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clinical Pharmacology		X	
Establishment Evaluation Request (EER)	X		
Pharmacology/Toxicology		X	
Methods Validation		X	
Environmental Assessment		X	
CDRH		X	
Other	X		Microbiology

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? Yes
CMC Filing Issues:
1. There was some discussion whether the paucity of stability data [REDACTED] (b) (4) would be grounds for “Refuse to File” since the Applicant had been clearly informed at the Pre-NDA meeting that 12 months’ data were expected with NDA submission. In addition, ONDQA policy is for all NDAs to be submitted with a minimum of 12 months long term stability data. However, since currently marketed KCl oral solution products are unapproved, ONDQA Management agreed that this application could be filed given the benefit of ultimately having an approved product with higher quality assurance available.

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? Yes
CMC Comments for 74-Day Letter:
Provide updated stability data for the drug product as soon as they are available.

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? Yes
Biopharmaceutics Filing Issues:
None

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? Yes
Biopharmaceutics Comments for 74-Day Letter:
<ul style="list-style-type: none">• Provide a table comparing the formulation (components and composition) of your proposed drug product vs. the formulations of each drug product used in the supportive PK references that you are relying on to support the approval of your proposed drug product. Provide a justification for any difference between the formulation of the proposed product and the oral solution formulations you are relying upon with respect to concentration, inactive ingredients, pH, and osmolality.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective?

Yes

Microbiology Filing Issues:

From: Miller, Denise
Sent: Friday, March 28, 2014 9:10 AM
To: Srinivasachar, Kasturi
Subject: RE: NDA 206814

It is fillable from my perspective and I will be requesting the report for the antimicrobial effectiveness testing that seems to be missing in the application.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
No	No	No	

Is a team review recommended?	No
Suggested expertise for team: No special expertise required. Drug substance information in DMF (b)(4) has been previously reviewed. Simple formulation and manufacturing process.	

Summary of Critical Issues and Complexities

Drug Substance:

- DMF (b)(4) was last reviewed on July 12, 2012 and found to be Adequate and there seem to be no Quality amendments since then. It is stated in the NDA that there are no known potential process impurities of potassium chloride but non-process impurities in the drug substance manufactured by (b)(4) are listed in Section 3.2.S.3.2. It is not clear if all these are routinely tested in the drug substance batches since many are not covered by the USP monograph. This issue should be evaluated.
- Is there a retest date for potassium chloride? There is no mention of this in the NDA.

Drug Product:

- The Applicant uses a (b)(4) method for assay. Have they established equivalence to the atomic absorption method in the USP monograph for potassium chloride oral solution? Is the potentiometric titration method better described as an alternate method since the USP procedure is always regarded as regulatory?
- Are the limits proposed in the specification for preservative content justified?
- pH is not monitored as part of the release specification or in the stability studies. Is this acceptable?
- Is the rationale for not routinely testing drug product batches for residual solvents acceptable?
- Has the extractables study on the container closure system been adequately performed?
- Can an expiration dating period of (b)(4) months be granted, as requested, based on the limited stability data available?

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

.Initial Quality Assessment

This is a 505(b)(2) application for a new dosage form, oral solution, of potassium chloride. Potassium chloride has previously been approved in other dosage forms – injection and extended release tablets or capsules. The reference listed product is K-DUR, potassium chloride extended release tablets, NDA 19439, approved in 1986. The Applicant is relying on the Agency’s finding of safety and efficacy for the RLD and consequently there are no pre-clinical or clinical studies in this application. Based on an evaluation of literature data comparing the bioavailability of solid oral dosage forms and oral solutions, a biowaiver from conducting bioequivalence studies is requested.

Only one meeting has been held with the Applicant – a pre-NDA teleconference on June 20, 2012 under PIND (b)(4). (b)(4) were proposed, a 10% oral solution and 20 mEq (b)(4).

The only CMC issue discussed was the extent of stability data that should be available at the time of NDA submission. The Applicant proposed submitting 3 registration batches with 6 months of both long term and accelerated data in the original NDA but was told that a complete data package should be submitted i.e. at least 12 months of long term and 6 months of accelerated data. The Applicant did not further discuss this issue.

Drug Substance: Potassium chloride is a white crystalline or colorless hygroscopic solid with a melting point of 773 °C . It is freely soluble in water, only slightly soluble in alcohol and insoluble in ether. It is manufactured by (b)(4) and a reference to their DMF (b)(4) for CMC information has been provided. It is stated in the NDA that there are no known process impurities of potassium chloride and that full details of non-process impurities are in the DMF. However, a tabular listing of potential non-process impurities with limits per EPA method 6010 has been submitted in the NDA. These are mainly (b)(4). Specifications based on the USP monograph for potassium chloride have been submitted to the NDA, however, it is mentioned that the DMF holder performs additional tests for (b)(4). Batch analysis data are provided for 3 batches of the drug substance used in the manufacture of the registration batches of drug product.

Drug Product: The proposed potassium chloride oral solutions, 20 mEq/15 mL and 40 mEq/15 ml are clear, orange colored, orange flavored liquids, packaged in (b)(4) mL white HDPE bottles (b)(4). The fill volume is 473 mL. The excipients in the formulation are glycerin, propylene glycol, methylparaben, propylparaben, sucralose, citric acid, natural and artificial orange flavor, FD&C Yellow #6 and purified water. All are compendial grade except the orange flavor and yellow color. The two strengths differ only in the composition of the active and the excipients. propylene glycol and purified water. CMC information for each strength has been provided in separate drug product sections. The manufacturer is Lehigh Valley Technologies in Allentown, PA.

The formulation development strategy is stated to be based on review of the literature, prior knowledge of the tested parameters, characteristics and performance of oral solution products as well as an evaluation of the currently marketed unapproved potassium chloride oral solution products. The critical characteristics of the formulation were determined to be preservative

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

content, preservative effectiveness, anti-oxidant/antimicrobial function, acceptable flavor, palatability and stability. The final formulation chosen was manufactured

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The same regulatory specifications are proposed for both strengths and consist of standard tests – appearance, identification, assay, preservative content and microbial limits. The limits and methods are based on the USP monograph for potassium chloride oral solution. Additional tests to those in USP are preservative content and microbial limits. Test results for 3 registration batches have been submitted.

Both strengths of the drug product are packaged in (b) (4) mL white HDPE bottles (b) (4)

(b) (4)

(b) (4)

An expiration dating period of 24 months is proposed for both strengths.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Additional Comments: Facilities for inspection have been entered in the EES database. Categorical exclusion from environmental assessment has been requested based on 21CFR 25.31(b). Methods Validation by FDA laboratories will not be requested at this time.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Biopharmaceutics Assessment

Submission: Pharma-Med, Inc. is seeking approval of Potassium Chloride Oral solution, USP, 20 mEq/15 mL, 40 mEq/15 mL for the treatment of patients with hypokalemia with or without metabolic alkalosis, (b) (4)

(b) (4) This 505 (b)(2) application relies on the previous findings of NDA 019439 for Potassium Chloride Extended Release Tablet 20 mEq (Schering).

Drug Product: The product under review is being proposed in two strengths, 20 mEq/15 mL and 40 mEq/15 mL. Both strengths have the same inactive ingredients, but differ in the amount of active ingredient (10% vs. 20%), propylene glycol (b) (4) and water (b) (4)

Pursuant to 21 CFR 320.22(a), 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 is included. In support of the biowaiver, published literature information on the bioavailability of unapproved oral solutions versus the approved extended release drug product is included in this submission. This literature information will be reviewed by OCP.

Review: The biopharmaceutics review will focus on the acceptability of the higher strength and formulation differences between the proposed oral solution and the solutions being used in the published BA studies (e.g. data from NDA 19123, NDA 19439).

Review Issues Identified: On a preliminary assessment, relying on CFR 320.22 (a) is incorrect since the product does not meet the requirements cited under this regulation. Since the dosage form of the approved product is an extended release oral tablet and the product under review is an oral formulation, a request for a biowaiver is not applicable.

However, based on CFR 320.24 (6), the use of the BA/BE data published in the literature *in lieu* of actual in vivo BA/BE generated by the Applicant may be adequate provided the published PK data are acceptable and a bridge between the formulation(s) used in each of the key PK publications and the proposed drug product is established.

Recommendation:

This NDA is fileable from the Biopharmaceutics perspective

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

FILING REVIEW CHECKLIST

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

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			NA

B. FACILITIES*				
* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential</i> filing issue or a <i>potential</i> review issue.				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA

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	Parameter	Yes	No	Comment
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

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	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

C. ENVIRONMENTAL ASSESMENT

	Parameter	Yes	No	Comment
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		

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D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		Cross-reference to DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			Cross-reference to DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?			Cross-reference to DMF (b) (4)
15.	Does the section contain controls for the DS?			Cross-reference to DMF (b) (4)
16.	Has stability data and analysis been provided for the drug substance?			Cross-reference to DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

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E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?			NA
23.	Have any biowaivers been requested?	X		
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		Limited stability data provided
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

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G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product			NA

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		See table below

DMF # (b) (4)	TYPE	HOLDER (b) (4)	ITEM REFERENCED	LOA DATE	COMMENTS
	II		Potassium Chloride	10-15-2013	
	III		(b) (4)	10-21-2013	
	III			10-30-2013	
	III			10-30-2013	
	III			10-23-2013	
	IV			10-23-2013	
	III			10-22-2013	

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

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Biopharmaceutics Filing Review Checklist

The following parameters are usually necessary to initiate a full Biopharmaceutics review (i.e., the NDA is complete enough to review but may have deficiencies). On **initial** overview of the NDA application for filing:

J. BIOPHARMACEUTICS				
	Parameter	Yes	No	Comment
34.	Does the application contain dissolution data?		X	NA. This is an oral solution.
35.	Is the dissolution test part of the DP specifications?		X	NA
36.	Does the application contain the dissolution method development report including data supporting the discriminating ability?		X	NA
37.	Is there a validation package for the analytical method and dissolution methodology?			NA
38.	Does the application include a biowaiver request?	X		There is a formal biowaiver request included in this submission. The biowaiver makes reference to CFR 320.22 (a)
39.	Is there information/data supporting the biowaiver request?	X		Published literature comparing the BA between unapproved potassium chloride oral solutions and the approved extended release tablet. The published references will be reviewed by OCP.
40.	Is there enough information to assess the extended release designation claim?		X	NA
41.	Does the application include an IVIVC model?		X	
42.	Does the application include information/data on in vitro alcohol dose-dumping potential?		X	NA
43.	Is there any <i>in vivo</i> BA or BE information in the submission?		X	
44.	Is there any design space proposed using in vitro release as a response variable?		X	This submission does not have QbD elements.
45.	Is the control strategy related to in vitro drug release?		X	NA

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K. Filing Conclusion				
	Parameter	Yes	No	Comment
46.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			Not applicable.
47.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			Not applicable.
48.	Are there any potential review issues identified?	X		<p>Potential Review Issues:</p> <p>On a preliminary assessment, relying of CFR 320.22 (a) is incorrect since the product does not meet the requirements cited under this regulation. Given that the dosage form of the approved product is an extended release oral tablet and the product under review is an oral formulation, the Applicant's request for a biowaiver is not applicable.</p> <p>However, based on CFR 320.24 (6), the use the BA/BE data published in the literature in lieu of actual in vivo BA/BE generated by the Applicant may be adequate provided the published PK data are acceptable and a bridge between the formulation(s) used in each of the key PK publications and the proposed drug product is established.</p>
49.	Are there any comments to be sent to the Applicant as part of the 74-Day letter?	X		Refer to page 3.
50.	Are there any internal comment to other disciplines:		X	The labeling indicates that the proposed drug product should be taken in the presence of food to avoid irritation. Since the effect of food is formulation dependent, the Applicant should provide information addressing this issue (from published literature or own studies).

**ONDQA Initial Quality Assessment (IQA) and Filing Review
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This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

{See appended electronic signature page}

Kasturi Srinivasachar, Ph.D

CMC-Lead or

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{See appended electronic signature page}

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

/s/

KASTURI SRINIVASACHAR
04/09/2014

SANDRA SUAREZ
04/09/2014

ANGELICA DORANTES
04/09/2014

OLEN M STEPHENS
04/09/2014