CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206814Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PATENT CERTIFICATION

21 CFR 314.50(i)(1)(ii)

In accordance with 21 CFR 314.50(i)(1)(ii), in the opinion and to the best knowledge of Pharma-Med, Inc, there are no patents that claim the drug or drugs on which investigations that are relied upon in this New Drug Application for potassium chloride oral solution, were conducted or that claim as use of such drug or drugs.

Nebiyou Getahoun, Ph.D.
President
Pharma-Med, Inc

January 03, 2014
Date

941 MARCON BLVD SUITE 301
ALLENTOWN PA 18109
Ph 610 443 1438 Fax 610 443 1459

EXCLUSIVITY SUMMARY

NDA # 206814 SUPPL # HFD # 110

Trade Name N/A

Generic Name Potassium Chloride Oral Solution

Applicant Name Pharma-Med

Approval Date, If Known: December 22, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES X NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO X

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The applicant established bioequivalence (by literature) with approved NDA 19439, Potassium Chloride Extended Release Tablets.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES ☐ NO X

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO X

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO X

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA

#(s).

NDA#	19439	KCl Oral Extended Release
NDA#	19123	KCl Oral Extended Release
NDA#	18238	KCl Oral Extended Release

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO X

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical

investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO X

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or

sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not

identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Edward Fromm, R.Ph., RAC
Title: Chief, Project Management Staff, Division of Cardiovascular and Renal Products
Date: 12/22/14

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D
Title: Director, Division of Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

EDWARD J FROMM
12/23/2014

NORMAN L STOCKBRIDGE
12/23/2014

PHARMA MED

DEBARMENT CERTIFICATION

Pursuant to Section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, as amended by the Generic Drug Enforcement Act of 1992, Pharma-Med, Inc., hereby certifies that it did not and will not use, in any capacity, the services of any person debarred under subsection (a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this NDA. This certification is based upon the list of debarred individuals available on the FDA website (http://www.fda.gov/ora/compliance_ref/debar/default.htm), last updated on 22 November 2013.

Nebiyou Getahoun

Nebiyou Getahoun, Ph.D.
President
Pharma-Med, Inc.

January 03, 2014
Date

261 MARCON BLVD SUITE 301
NORTHAMPTON PA 18067
Ph 610 443-1438 Fax 610-443-1459

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 206814 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: 7
Proprietary Name: N/A Established/Proper Name: Potassium Chloride Dosage Form: Oral Solution		Applicant: Pharma-Med Agent for Applicant (if applicable): Melissa L. Goodhead
RPM: Edward Fromm		Division: Division of Cardiovascular and Renal Products

NDAs and NDA Efficacy Supplements:

NDA Application Type: 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

NDA 19439 (Potassium Chloride Extended Release Tablets)

Provide a brief explanation of how this product is different from the listed drug.

Product above is an Extended Release Tablet vs. Oral Solution for NDA

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☒ No changes ☐ Updated Date of check: 12/22/14

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is: **December 27, 2014**	X AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	X None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	Not Applicable
❖ Application Characteristics [3]	

Review priority: X Standard ☐ Priority
Chemical classification (new NDAs only): 1

☐ Fast Track
☐ Rolling Review
Orphan drug designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	**X** Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	X No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	X No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	**X** Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☒ N/A (no paragraph IV certification) ☐ Verified

Version: 1/27/12

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[4]	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	X Included
Documentation of consent/non-consent by officers/employees	X Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Included
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	12-8-14
• Original applicant-proposed labeling	Included
• Example of class labeling, if applicable	Included

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	NA
• Original applicant-proposed labeling	NA
• Example of class labeling, if applicable	NA
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	October 30,2014
❖ Proprietary Name • Acceptability/non-acceptability letter(s) • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	NA
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ DMEPA October 24 and November 19, 2014 ☒ ODPD (DDMAC) 12-19-14 ☐ SEALD N/A ☐ CSS Not Applicable ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	RPM Filing Review- April 18, 2014, RPM Overview-12/29/14 ☒ November 26, 2014 ☒ November 26, 2014
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	X Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes X No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes X No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC December 17, 2014 If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	X Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	74 day letter- April 25, 2014
❖ Internal memoranda, telecons, etc.	N/A
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	X No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	X N/A
• Pre-NDA/BLA meeting *(indicate date of mtg)*	N/A
• EOP2 meeting *(indicate date of mtg)*	NA
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	Pre-IND Mtg- June 20, 2012
❖ Advisory Committee Meeting(s)	X No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None
Division Director Summary Review *(indicate date for each review)*	☒ December 22, 2014
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ December 12, 2014
PMR/PMC Development Templates *(indicate total number)*	☒ 1
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	NA
• Clinical review(s) *(indicate date for each review)*	NA
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	X None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☒ and include a review/memo explaining why not *(indicate date of review/memo)*	NA-no clinical studies were needed or submitted for this NDA
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	NA
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	NA
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	NA ☐

[6] Filing reviews should be filed with the discipline reviews.

❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ NA
Clinical Microbiology X None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None see cosigned review below.
Clinical Pharmacology review(s) *(indicate date for each review)*	☒ October 9, 2014
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None
Nonclinical ☒ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	NA
❖ ECAC/CAC report/memo of meeting	NA
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	NA
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None-see cosigned review below
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	Product Quality-October 27 and December 9, 2014 Biopharmaceutics-October 10, 2014
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ October 24, 2014
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	X None

Version: 1/27/12

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	October 27, 2014 (see Product Quality Review)
☐ Review & FONSI *(indicate date of review)*	Not applicable
☐ Review & Environmental Impact Statement *(indicate date of each review)*	Not applicable
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: December 9, 2014 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s ADRA.

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/s/

EDWARD J FROMM
12/29/2014

PeRC PREA Subcommittee Meeting Minutes
December 17, 2014

PeRC Members Attending:
Lynne Yao
Wiley Chambers
George Greeley
Lily Mulugeta
Dianne Murphy
Greg Reaman
Hari Cheryl Sachs
Michelle Roth-Cline
Tom Smith
Suresh Pagay
Karen Davis-Bruno
Olivia Ziolkowski
Rosemary Addy
Barbara Buch
(b) (4)
Barbara Buch
Peter Starke

PREA

[redacted]

10:50	NDA	206814	Potassium Chloride (Assessment)	(1) _ Potassium Chloride is indicated for the treatment of patients with hypokalemia with or without metabolic alkalosis.[redacted] (2) ___[redacted]

[redacted]

[redacted]

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/s/

GEORGE E GREELEY
01/05/2015

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Dear Review Division:

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Complete the section(s) of this template that are relevant to your *current submission.*

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Full Waiver *– On its own initiative or at the request of an applicant, FDA may waive the requirement for a pediatric assessment for all pediatric age groups if: (1) studies would be impossible or highly impracticable; (2) there is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups; or (3) the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, AND is not likely to be used in a substantial number of pediatric patients. If studies are being waived because there is evidence that the product would be ineffective or unsafe in all pediatric age groups, this information MUST be included in the pediatric use section of labeling.*

Partial Waiver *– FDA may waive the requirement for a pediatric assessment for a specific pediatric age group if any of the criteria for a full waiver are met for that age group or if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed. If a partial waiver is granted because a pediatric formulation cannot be developed, the partial waiver will only cover the pediatric groups requiring that formulation.*

Pediatric Assessment *– The pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required. It also includes data that are adequate to: (1) assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations; and (2) support dosing and administration for each pediatric subpopulation for which the data support a finding that the product is safe and effective.*

Pediatric Plan *– A pediatric plan is the applicant's statement of intent describing the planned or ongoing pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that they plan to conduct or are conducting (i.e., the pediatric studies that will comprise the pediatric assessment). If necessary, the plan should address the development of an age-appropriate formulation and must contain a timeline for the completion of studies. FDA recommends that the timeline should include the dates the applicant will: (1) submit the protocol; (2) complete the studies; and 3) submit the study reports.*

Pediatric Population/Patient- *21 CFR 201.57 defines pediatric population (s) and pediatric patient (s) as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.*

PREA Pediatric Record/Pediatric Page *– The pediatric record is completed for all NDAs, BLAs, or supplemental NDAs or BLAs. This record indicates whether the application triggers the Pediatric Research Equity Act (PREA), and if so, indicates how pediatric studies will be or have been addressed for each pediatric age group. If the Agency is waiving or deferring any or all pediatric studies, the pediatric record also includes the reason(s) for the waiver and/or deferral. (Note that with the implementation of DARRTS, the Pediatric Record is replacing the Pediatric Page for NDAs. The Pediatric Page is still to be used for BLAs.) For NDAs, the information should be entered into DARRTS and then the form should be created and submitted along with other required PeRC materials. Divisions should complete the Pediatric Page for NDAs that do not trigger PREA and submit the Pediatric Page via email to CDER PMHS until further notice.*

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND

Please check all that apply: ☐ **Full Waiver** ☐ **Partial Waiver** ☒ **Pediatric Assessment** ☐ **Deferral/Pediatric Plan**

BLA/NDA#: 206814

PRODUCT PROPRIETARY NAME: N/A **ESTABLISHED/GENERIC NAME: Potassium chloride oral solution**

APPLICANT/SPONSOR: Pharma-Med, Inc.

PREVIOUSLY APPROVED INDICATION/S:
(1) **None**
(2) _____
(3) _____
(4) _____

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

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(2)

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_____
_____
(3) _____
(4) _____

NDA STAMP DATE: 2/27/14

PDUFA GOAL DATE: 12/27/14

SUPPLEMENT TYPE: N/A

SUPPLEMENT NUMBER: N/A

Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

NEW ☐ ***active ingredient(s) (includes new combination);*** ☐ ***indication(s);*** ☒ ***dosage form;*** ☒ ***dosing regimen; or*** ☐ ***route of administration?***

Did the sponsor submit an Agreed iPSP? Yes ☐ ***No*** ☒

Did FDA confirm its agreement to the sponsor's Agreed iPSP? Yes ☐ ***No*** ☒

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes ☐ ***No*** ☒

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes ☐ ***No*** ☒

If Yes, PMR #_____ NDA #_____

Does the division agree that this is a complete response to the PMR? Yes ☐ ***No*** ☐

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.

WAIVER REQUEST

Please attach:

☒ ***Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.***

☐ ***Pediatric Record***

1. Pediatric age group(s) to be waived. **N/A**

2. Reason(s) for waiving pediatric assessment requirements (***Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for <u>each</u> age group or indication. This section should reflect the Division's thinking.***)

   ☐ Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from the adult-related conditions on the next page.

   ☐ The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information MUST be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.

   ☐ The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **<u>and</u>** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

   ☐ Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted. ***(This reason is for Partial Waivers Only)***

3. Provide justification for Waiver:

Although the applicant requested a waiver, they also submitted literature to support their proposed pediatric labeling.

We believe this literature, in addition to the bridge established in adults between their formulation and various types of modified release products is sufficient to provide adequate instructions for use in children (all ages).

3. Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:

The applicant's proposed language is as follows:

Pediatric Use

Safety and effectiveness in pediatric patients has not been conducted in controlled studies. However, a review of data from peer reviewed literature recommends a dosing for infants/children, ages 3 months to 18 years of 1 to 4 mEq/kg/day, delivered in divided doses, but not to exceed 1 to 2 mEq/kg/dose. Maintenance dosing should not exceed 3 mEq/kg/day. Individualize the dose based upon serum potassium levels.

We propose the following language:

Pediatric Use

The safety and effectiveness of Potassium Chloride in children up to18 years is supported by substantial evidence from adequate and well-controlled studies of Potassium Chloride in adults, and infants/children with diarrhea and malnutrition, with the limitation that studies have not reported data on infants less than 1 month of age. Data from peer reviewed literature recommend dosing regimens for infants/children, ages (b) (4) months to (b) (4) years of (b) (4) to 4 mEq/kg/day, delivered in divided doses, not to exceed 1 (b) (4) mEq/kg/dose. Individual doses should not exceed 20 mEq. Maintenance dosing should not exceed 3 mEq/kg/day. Individualize the dose based upon serum potassium levels. .Maximum dosing in children should be (b) (4) mEq/day in divided doses.

Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics
These conditions qualify for waiver because studies would be impossible or highly impractical.

- actinic keratosis
- adjunctive treatment of major depressive disorder
- age-related macular degeneration
- Alzheimer's disease
- amyloidosis
- amyotrophic lateral sclerosis
- androgenic alopecia
- atherosclerotic cardiovascular disease
- autosomal dominant polycystic kidney disease (ADPKD)
- benign monoclonal gammopathy
- benign prostatic hyperplasia
- cancer:
  - basal cell and squamous cell skin cancer
  - bladder
  - breast
  - cervical
  - colorectal
  - endometrial
  - esophageal
- cancer (continued):
  - follicular lymphoma
  - gastric
  - hairy cell leukemia
  - hepatocellular
  - indolent non-Hodgkin lymphoma
  - lung (small & non-small cell)
  - multiple myeloma
  - oropharynx (squamous cell)
  - ovarian (non-germ cell)
  - pancreatic
  - prostate
  - refractory advanced melanoma
  - renal cell
  - uterine
- chronic lymphocytic leukemia
- chronic obstructive pulmonary disease
- cryoglobulinemia
- diabetic peripheral neuropathy / macular edema

digestive disorders (gallstones)

dry eye syndrome (keratoconjunctivitis sicca)

erectile dysfunction

essential thrombocytosis

Huntington's chorea

infertility & reproductive technology

ischemic vascular diseases, such as angina, myocardial infarction, and ischemic stroke

memory loss

menopause and perimenopausal disorders

mesothelioma

myelodysplasia

myelofibrosis & myeloproliferative disorders

osteoarthritis

overactive bladder

Parkinson's disease

paroxysmal nocturnal hemoglobinuria

plasma cells and antibody production disorders

polycythemia vera

postmenopausal osteoporosis

prevention of stroke and systemic embolic events in atrial fibrillation

psoriatic arthritis

reduction of thrombotic cardiovascular events in patients with coronary artery disease

replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone

retinal vein occlusions

stress urinary incontinence

temporary improvement in the appearance of caudal lines

treatment of incompetent great saphenous veins and varicosities

type 2 diabetic nephropathy

vascular dementia/vascular cognitive disorder/impairment

DEFERRAL REQUEST

Please attach:

☐ ***Pediatric Record***

1. **Age groups included in the deferral request:**

2. **Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request:**

3. **Reason/s for requesting deferral of pediatric studies in pediatric patients with disease:** (***Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for <u>each</u> age group or indication. This section should reflect the Division's thinking.***)

   a. Adult studies are completed and ready for approval
   b. Additional safety or effectiveness data needed (**describe**)
   c. Other (**specify**)

4. **Provide projected date for the submission of the pediatric assessment (deferral date):**

5. **Did applicant provide certification of grounds for deferring assessments?** ☐ **Yes** ☐ **No**

6. **Did applicant provide evidence that studies will be done with due diligence and at the earliest possible time?** ☐ **Yes** ☐ **No**

SPONSOR'S PROPOSED PEDIATRIC PLAN

1. **Has a pediatric plan been submitted to the Agency?** ☐ **Yes** ☐ **No**

2. Does the division agree with the sponsor's plan? ☐ **Yes** ☐ **No**

3. **Did the sponsor submit a timeline for the completion of studies (must include at least dates for protocol submission, study completion and studies submitted)?** ☐ **Yes** ☐ **No**

a. **Protocol Submission:**
b. **Study Completion:**
c. **Study Submission:**

4. **Has a Written Request been issued? ☐ Yes ☐ No (If yes and the WR matches the proposed pediatric plan, please attach a copy. It is not necessary to complete the remainder of this document)**

5. **Has a PPSR been submitted? ☐ Yes ☐ No (If yes, you may submit a draft WR and have PeRC review WR and deferral/plan at the same time.)**

Please note that the remainder of this section should be completed based on what the Division is requiring regardless of what the sponsor is proposing.

DIVISION'S PROPOSED PK, SAFTEY, AND EFFICACY TRIAL

Please complete as much of the information below as possible. Please note that the portions of the document that are shaded are not required for early stage pediatric plans but are useful if available.

Types of Studies/Study Design:

Nonclinical Studies:

Clinical Studies:

Age group and population (indication) in which study will be performed:
This section should list the age group and population exactly as it is in the plan.

Example:
Study 1: patients aged X to Y years.
Study 2: sufficient number of subjects to adequately characterize the pharmacokinetics in the above age groups.

Number of patients to be studied or power of study to be achieved:

Example:
Study 1: X subjects in each treatment arm and be powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% must be females and 25% must be less than 3 years.

Study 2: This study is powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters.

Entry criteria:
This section should list pertinent inclusion/exclusion criteria.

Example:
Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs
Patients must have a negative pregnancy test if female..

Clinical endpoints:

Example:
Study 1: Clinical outcome and safety will be the primary endpoints.

Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG should attempt to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F.

Timing of assessments:

Example :baseline, week 1, 4, and 6

Statistical information (statistical analyses of the data to be performed):
Example:
Study 1 non-inferiority: two-sided 95% confidence interval (CI) of treatment difference in improvement rates should be within 25% of the control's response rate.

Study 2: descriptive statistical methods for AUC, C max, Tmax, Cl/F and compared to adults.

Division comments on product safety:
Are there any safety concerns currently being assessed? ☐ **Yes** ☐ **No**

Are there safety concerns that require us to review post-marketing safety data before fully designing the pediatric studies? ☐ **Yes** ☐ **No**

Will a DSMB be required? ☐ **Yes** ☐ **No**

Other comments:

Division comments on product efficacy:

Division comments on sponsor proposal to satisfy PREA:

PeRC ASSESSMENT TEMPLATE

Please attach:

- ☐ ***Proposed Labeling from the sponsor unless the Division plans to change. If changing the language, include the appropriate language at the end of this form. The Division has not yet revised the sponsor's proposed labeling.***
- ☐ ***Pediatric Record***

Date of PREA PMR:
Description of PREA PMR: ***(Description from the PMC database is acceptable)***

Was Plan Reviewed by PeRC? ☐ **Yes** ☐ **No** If yes, did sponsor follow plan?

If studies were submitted in response to the Written Request (WR), provide the annotated WR in lieu of completing the remainder of the Pediatric Assessment template.

Indication(s) that were studied:
This section should list the indication(s) exactly as written in the *protocols.*

Example:
DRUG for the treatment of the signs and symptoms of disease x.

Number of Centers _____

Number and Names of Countries _____

Drug information:

Examples in italics

- **Route of administration**: *Oral*
- ***Formulation:** *disintegrating tablet*
- **Dosage:** *75 and 50 mg*
- **Regimen:** *list frequency of dosage administration*

**If the dosage form is powder for oral suspension; provide information on storage statement and concentration after reconstitution (e.g. with water, juice or apple sauce etc.)*
Types of Studies/ Study Design: *Example:* *Study 1: Multi- center, randomized, active controlled double blind study to evaluate the safety and efficacy of (drug name, concentration, form etc) DRUG administered twice daily for the treatment of patients with disease x.* *Study 2: PK and safety study of (drug name, concentration, form etc) DRUG in patients with disease x.*
Age group and population in which study/ies was/were performed: *Example:* *Study 1: patients aged X to Y years.* *Study 2: sufficient number of patients to adequately characterize the pharmacokinetics in the above age groups.*
Number of patients studied or power of study achieved: *Example:* *Study 1: X patients in each treatment arm and was powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% were females and 25% were less than 3 years.* ***Study 2: powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters. The study included at least X evaluable patients. .***
Entry criteria: This section should list pertinent inclusion/exclusion criteria. *Example:* *Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs* *Patients had a negative pregnancy test if female.*

Clinical endpoints: *Example:* *Study 1: Clinical outcome and safety were the primary endpoints.* *Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG attempted to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F*
Statistical information (statistical analyses of the data performed): This section should list the statistical tests conducted. *Example:* *Study 1 - two-sided 95% confidence interval (CI) of treatment difference in improvement rates were within 25% of the control's response rate.* *Study 2: descriptive statistical methods for AUC, C max, Tmax, Cl/F and compared to adults.*
Timing of assessments: *Example:* *Baseline, week 2, week, 6, and end of treatment*

Division comments and conclusions (Summary of Safety and Efficacy)
Provide language Review Division is proposing for the appropriate sections of the label if different from sponsor-proposed language.

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

/s/

EDWARD J FROMM
12/09/2014

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Pediatric Plan *– A pediatric plan is the applicant's statement of intent describing the planned or ongoing pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that they plan to conduct or are conducting (i.e., the pediatric studies that will comprise the pediatric assessment). If necessary, the plan should address the development of an age-appropriate formulation and must contain a timeline for the completion of studies. FDA recommends that the timeline should include the dates the applicant will: (1) submit the protocol; (2) complete the studies; and 3) submit the study reports.*

Pediatric Population/Patient*- 21 CFR 201.57 defines pediatric population (s) and pediatric patient (s) as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.*

PREA Pediatric Record/Pediatric Page *– The pediatric record is completed for all NDAs, BLAs, or supplemental NDAs or BLAs. This record indicates whether the application triggers the Pediatric Research Equity Act (PREA), and if so, indicates how pediatric studies will be or have been addressed for each pediatric age group. If the Agency is waiving or deferring any or all pediatric studies, the pediatric record also includes the reason(s) for the waiver and/or deferral. (Note that with the implementation of DARRTS, the Pediatric Record is replacing the Pediatric Page for NDAs. The Pediatric Page is still to be used for BLAs.) For NDAs, the information should be entered into DARRTS and then the form should be created and submitted along with other required PeRC materials. Divisions should complete the Pediatric Page for NDAs that do not trigger PREA and submit the Pediatric Page via email to CDER PMHS until further notice.*

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND

Please check all that apply: ☒ **Full Waiver** ☐ **Partial Waiver** ☐ **Pediatric Assessment** ☐ **Deferral/Pediatric Plan**

BLA/NDA#: 206814

PRODUCT PROPRIETARY NAME: N/A **ESTABLISHED/GENERIC NAME: Potassium chloride oral solution**

APPLICANT/SPONSOR: Pharma-Med, Inc.

PREVIOUSLY APPROVED INDICATION/S:
(1) **_treatment of hypokalemia_____**
(2) **_____**
(3) **_____**
(4) **_____**

PROPOSED INDICATION/S:
(1) **_treatment of hypokalemia _____**
(2) **_____**
(3) **_____**
(4) **_____**

NDA STAMP DATE: 2/27/14

PDUFA GOAL DATE: 12/27/14

SUPPLEMENT TYPE: N/A

SUPPLEMENT NUMBER: N/A

Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

NEW ☐ active ingredient(s) (includes new combination); ☐ indication(s); ☒ dosage form; ☐ dosing regimen; or ☐ route of administration?

Did the sponsor submit an Agreed iPSP? Yes ☐ No ☒

Did FDA confirm its agreement to the sponsor's Agreed iPSP? Yes ☐ No ☒

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes ☐ No ☒

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes ☐ No ☒

If Yes, PMR # _____ NDA # _____

Does the division agree that this is a complete response to the PMR? Yes ☐ No ☐

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.

WAIVER REQUEST

Please attach:

☒ ***Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.***

☐ ***Pediatric Record***

1. Pediatric age group(s) to be waived. **All age groups.**

2. Reason(s) for waiving pediatric assessment requirements (***Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for <u>each</u> age group or indication. This section should reflect the Division's thinking.***)

   ☐ Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from the adult-related conditions on the next page.

   ☐ The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information MUST be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.

   ☐ The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **<u>and</u>** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

   ☐ Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted***. (This reason is for Partial Waivers Only)***

3. *Provide justification for Waiver:* **Although the sponsor officially requested a waiver, they also provided literature to support their proposed pediatric labeling, (the sponsor also did not provide any reasoning to support a waiver). The Division believes that we can provide adequate instructions for use based on the submitted literature.**

3. *Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:*
The sponsor's proposed language is as follows (the Division has not attempted to revise this language yet):

(b) (4)

Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics

These conditions qualify for waiver because studies would be impossible or highly impractical.

- actinic keratosis
- adjunctive treatment of major depressive disorder
- age-related macular degeneration
- Alzheimer's disease
- amyloidosis
- amyotrophic lateral sclerosis
- androgenic alopecia
- atherosclerotic cardiovascular disease
- autosomal dominant polycystic kidney disease (ADPKD)
- benign monoclonal gammopathy
- benign prostatic hyperplasia
- cancer:
  - basal cell and squamous cell skin cancer
  - bladder
  - breast
  - cervical
  - colorectal
  - endometrial
  - esophageal
- cancer (continued):
  - follicular lymphoma
  - gastric
  - hairy cell leukemia
  - hepatocellular
  - indolent non-Hodgkin lymphoma
  - lung (small & non-small cell)
  - multiple myeloma
  - oropharynx (squamous cell)
  - ovarian (non-germ cell)
  - pancreatic
  - prostate
  - refractory advanced melanoma
  - renal cell
  - uterine
- chronic lymphocytic leukemia
- chronic obstructive pulmonary disease
- cryoglobulinemia
- diabetic peripheral neuropathy / macular edema

digestive disorders (gallstones)

dry eye syndrome (keratoconjunctivitis sicca)

erectile dysfunction

essential thrombocytosis

Huntington's chorea

infertility & reproductive technology

ischemic vascular diseases, such as angina, myocardial infarction, and ischemic stroke

memory loss

menopause and perimenopausal disorders

mesothelioma

myelodysplasia

myelofibrosis & myeloproliferative disorders

osteoarthritis

overactive bladder

Parkinson's disease

paroxysmal nocturnal hemoglobinuria

plasma cells and antibody production disorders

polycythemia vera

postmenopausal osteoporosis

prevention of stroke and systemic embolic events in atrial fibrillation

psoriatic arthritis

reduction of thrombotic cardiovascular events in patients with coronary artery disease

replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone

retinal vein occlusions

stress urinary incontinence

temporary improvement in the appearance of caudal lines

treatment of incompetent great saphenous veins and varicosities

type 2 diabetic nephropathy

vascular dementia/vascular cognitive disorder/impairment

DEFERRAL REQUEST N/A

Please attach:

☐ ***Pediatric Record***

1. **Age groups included in the deferral request:**

2. **Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request:**

3. **Reason/s for requesting deferral of pediatric studies in pediatric patients with disease:** (***Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for <u>each</u> age group or indication. This section should reflect the Division's thinking.***)

   a. Adult studies are completed and ready for approval
   b. Additional safety or effectiveness data needed (**describe**)
   c. Other (**specify**)

4. **Provide projected date for the submission of the pediatric assessment (deferral date):**

5. **Did applicant provide certification of grounds for deferring assessments?** ☐ **Yes** ☐ **No**

6. **Did applicant provide evidence that studies will be done with due diligence and at the earliest possible time?** ☐ **Yes** ☐ **No**

SPONSOR'S PROPOSED PEDIATRIC PLAN

1. **Has a pediatric plan been submitted to the Agency?** ☐ **Yes** ☐ **No**

2. Does the division agree with the sponsor's plan? ☐ **Yes** ☐ **No**

3. **Did the sponsor submit a timeline for the completion of studies (must include at least dates for protocol submission, study completion and studies submitted)?** ☐ **Yes** ☐ **No**

a. **Protocol Submission:**
b. **Study Completion:**
c. **Study Submission:**

4. **Has a Written Request been issued? ☐ Yes ☐ No (If yes and the WR matches the proposed pediatric plan, please attach a copy. It is not necessary to complete the remainder of this document)**

5. **Has a PPSR been submitted? ☐ Yes ☐ No (If yes, you may submit a draft WR and have PeRC review WR and deferral/plan at the same time.)**

Please note that the remainder of this section should be completed based on what the Division is requiring regardless of what the sponsor is proposing.

DIVISION'S PROPOSED PK, SAFTEY, AND EFFICACY TRIAL

Please complete as much of the information below as possible. Please note that the portions of the document that are shaded are not required for early stage pediatric plans but are useful if available.

Types of Studies/Study Design:

Nonclinical Studies:

Clinical Studies:

Age group and population (indication) in which study will be performed:
This section should list the age group and population exactly as it is in the plan.

Example:
Study 1: patients aged X to Y years.
Study 2: sufficient number of subjects to adequately characterize the pharmacokinetics in the above age groups.

Number of patients to be studied or power of study to be achieved:

Example:
Study 1: X subjects in each treatment arm and be powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% must be females and 25% must be less than 3 years.

Study 2: This study is powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters.

Entry criteria:
This section should list pertinent inclusion/exclusion criteria.

Example:
Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs
Patients must have a negative pregnancy test if female..

Clinical endpoints:

Example:
Study 1: Clinical outcome and safety will be the primary endpoints.

Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG should attempt to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F.

Timing of assessments:

Example :baseline, week 1, 4, and 6

Statistical information (statistical analyses of the data to be performed):
Example:
Study 1 non-inferiority: two-sided 95% confidence interval (CI) of treatment difference in improvement rates should be within 25% of the control's response rate.

Study 2: descriptive statistical methods for AUC, C max, Tmax, Cl/F and compared to adults.

Division comments on product safety:
Are there any safety concerns currently being assessed? ☐ **Yes** ☐ **No**

Are there safety concerns that require us to review post-marketing safety data before fully designing the pediatric studies? ☐ **Yes** ☐ **No**

Will a DSMB be required? ☐ **Yes** ☐ **No**

Other comments:

Division comments on product efficacy:

Division comments on sponsor proposal to satisfy PREA:

PeRC ASSESSMENT TEMPLATE

Please attach:

☐ ***Proposed Labeling from the sponsor unless the Division plans to change. If changing the language, include the appropriate language at the end of this form. The Division has not yet revised the sponsor's proposed labeling.***

☐ ***Pediatric Record***

Date of PREA PMR:
Description of PREA PMR: ***(Description from the PMC database is acceptable)***

Was Plan Reviewed by PeRC? ☐ **Yes** ☐ **No** If yes, did sponsor follow plan?

If studies were submitted in response to the Written Request (WR), provide the annotated WR in lieu of completing the remainder of the Pediatric Assessment template.

Indication(s) that were studied:
This section should list the indication(s) exactly as written in the *protocols.*

Example:
DRUG for the treatment of the signs and symptoms of disease x.

Number of Centers _____

Number and Names of Countries _____

Drug information:

Examples in italics

- **Route of administration**: *Oral*
- ***Formulation:** *disintegrating tablet*
- **Dosage:** *75 and 50 mg*
- **Regimen:** *list frequency of dosage administration*

**If the dosage form is powder for oral suspension; provide information on storage statement and concentration after reconstitution (e.g. with water, juice or apple sauce etc.)*

Types of Studies/ Study Design:
Example:
Study 1: Multi- center, randomized, active controlled double blind study to evaluate the safety and efficacy of (drug name, concentration, form etc) DRUG administered twice daily for the treatment of patients with disease x.
Study 2: PK and safety study of (drug name, concentration, form etc) DRUG in patients with disease x.

Age group and population in which study/ies was/were performed:

Example:
Study 1: patients aged X to Y years.
Study 2: sufficient number of patients to adequately characterize the pharmacokinetics in the above age groups.

Number of patients studied or power of study achieved:
Example:
Study 1: X patients in each treatment arm and was powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% were females and 25% were less than 3 years.

Study 2: powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters. The study included at least X evaluable patients. .

Entry criteria:
This section should list pertinent inclusion/exclusion criteria.

Example:
Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs
Patients had a negative pregnancy test if female.

Clinical endpoints: *Example:* *Study 1: Clinical outcome and safety were the primary endpoints.* *Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG attempted to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F*
Statistical information (statistical analyses of the data performed): This section should list the statistical tests conducted. *Example:* *Study 1 - two-sided 95% confidence interval (CI) of treatment difference in improvement rates were within 25% of the control's response rate.* *Study 2: descriptive statistical methods for AUC, C max, Tmax, Cl/F and compared to adults.*
Timing of assessments: *Example:* *Baseline, week 2, week, 6, and end of treatment*

Division comments and conclusions (Summary of Safety and Efficacy)
Provide language Review Division is proposing for the appropriate sections of the label if different from sponsor-proposed language.

1.9 Pediatric Administrative Information
[Potassium Chloride Oral Solution, USP, 20 mEq/15 mL, 40 mEq/15 mL]

1.9.1 Request for Waiver of Pediatric Studies
[Potassium Chloride Oral Solution, USP, 20 mEq/15 mL, 40 mEq/15 mL]

1.9 Pediatric Administrative Information

1.9.1 Request for Waiver of Pediatric Studies

Request for a Waiver of the Pediatric Research Equity Act (PREA) Requirement

Objective and Summary of the Safety Findings in Children:

Pharma-Med, Inc. is submitting a 505(b)(2) New Drug Application for a 10% potassium chloride oral solution (20 mEq/15 ml) and a 20% potassium chloride oral solution (40 mEq/15 ml) for the treatment and/or prevention of hypokalemia. The current document is provided in support of a waiver of the Pediatric Research Equity Act (PREA) requirement for this product. A literature search was conducted to evaluate available information on pediatric use of K^+ supplements with regard to efficacy and safety data from previous clinical trials that would support this waiver request. Literature search terms included Potassium or Potassium Chloride (sub-terms: Administration & Dosage, Pharmacokinetics, Pharmacology, Physiology, Standards, Therapeutic Use, and Therapy) combined with Clinical Trials or Hypokalemia (sub-term: Drug Therapy) or Fluid Therapy (sub-terms: Methods, Standards, Statistics & Numerical Data, Trends, and Utilization). An additional search was conducted that included the keywords Potassium Chloride and Fluid Therapy. A focused search for safety-related information was also conducted using the search terms Potassium Chloride (sub-terms: Adverse Effects, Poisoning, and Toxicity). A search for information on excretion was conducted using the search terms Potassium Chloride (sub-terms: Metabolism, Secretion, and Urine) combined with keyword Excretion. All searches were limited to full text, English language, and child (0 to 18 years) with no date range limits applied. Databases searched for potentially relevant literature include Medline, Embase, Biosis, Google Scholar, PsycINFO, Derwent Drug File, and Current Contents.

The literature supports the use of oral K^+ supplements for the treatment and/or prevention of hypokalemia. In fact, oral administration of K^+ supplements is the preferable method of treatment for hypokalemia (Tschudy et al.,2012, Kliegman et al., 2011, Rudolph, 2011,

American Society of Hospital Pharmacists [ASHP], 2013), since parenteral intravenous (IV) administration is associated with high risk of iatrogenic hyperkalemia (Tschudy et al., 2012). In some cases, where IV administration is indicated as initial treatment, it is recommended that oral supplements replace parenteral therapy as soon as possible (ASHP, 2013). Recommended doses of K^+ supplements vary widely; however, most authors agree that acceptable dose ranges for children are from 1 to 4 mEq/kg/day divided into two or three doses (Tschudy et al., Kliegman et al., 2011, Rudolph, 2011, ASHP, 2013), and maintenance doses in children should not exceed 3 mEq/kg/day (ASHP, 2013).

A review of published literature has shown that seven controlled clinical trials were conducted in children to evaluate efficacy and safety of various oral rehydration salt (ORS) electrolyte solutions used for the treatment of diarrhea. One additional controlled study was conducted with an oral KCl supplement in 99 children with Kwashiorkor. A summary of this latter study is included because of the positive effects of elevated K^+ on mortality in this disorder. In the seven rehydration trials, the ORS formulation was examined alongside the standard World Health Organization (WHO) ORS solution, used as a comparator. The current recommended composition of the WHO ORS for the treatment of childhood diarrhea is as follows: 20 mmol/L (20 mEq K^+) of K^+, 75 mmol/L Na^+, 75 mmol/L anhydrous glucose, 65 mmol/L Cl^-, 10 mmol/L citrate, and a total osmolarity of 245 mOsmol/L. However, at the time that many of these controlled trials were conducted, recommended Na^+ (90 mmol/L) and glucose (111 mmol/L) concentrations and the osmolarity (311 mOsmol/L) of the standard WHO ORS solution were slightly higher than the current standard.

While the efficacy results reported by each of the rehydration clinical trials [1-3, 5-8] varies with each of the ORS solutions tested, in general, the safety data from these clinical trials support the conclusion that ORS solutions containing KCl concentrations up to 35 mmol/L (35 mEq/L) are well-tolerated in children, with comparable safety to that observed with the standard WHO ORS solution, regardless of osmolarity or content of Na^+ or glucose. Below is a brief summary of the results of each of the controlled rehydration trials and one controlled study in children with Kwashiorkor that is offered as support of a waiver of the PREA requirement for the Pharma-Med 10% potassium chloride oral solution (20 mEq/15 ml) and 20% potassium chloride oral solution (40 mEq/15 mL).

As previously discussed in Pharma-Med's June 20, 2012 meeting with the FDA, Division of Cardiovascular and Renal Products (minutes attached), and in accordance with 21 CFR 314.55, Pharma-Med, Inc. herewith requests a full waiver of the requirement for a pediatric assessment (PREA) of Potassium Chloride Oral Solution, USP. Pharma-Med, Inc. has provided, herein, the literature-based support for this waiver and has utilized this literature to develop adequate instructions for use in pediatric patients.

Nebiyou Getahoun

Nebiyou Getahoun, Ph.D.
President
Pharma-Med, Inc.

03-31-2014
Date

16 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

RUSSELL FORTNEY
10/29/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM: Russell Fortney, DCRP (6-1068)
Mail: OSE	

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
10/27/14		**206814**	**NDA**	2/27/14

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Potassium chloride oral solution	S	7	**11/27/14**

NAME OF FIRM: **Pharma-Med, Inc.**

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: DCRP would like to know what adverse events have been reported for oral potassium chloride products (approved and/or marketed unapproved products) given to children aged birth to 18 years of age. Please search for such reports for 2009 through 2014 and provide dose administered and amount of diluent used if that information is available.

While the current product is not marketed, there have been other unapproved potassium chloride oral solutions (and powders for oral solution) that have been marketed.

For questions about this consult please contact Russell Fortney (Project Manager) or Melanie Blank (Clinical Reviewer).

The PDUFA goal date for this application is 12/27/14

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check all that apply) ☒ DARRTS ☐ HAND
SIGNATURE OF RECEIVER Russell Fortney	SIGNATURE OF DELIVERER

06/18/2013

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/s/

RUSSELL FORTNEY
10/28/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206814

DISCIPLINE REVIEW LETTER

Pharma-Med, Inc.
Attention: Melissa L. Goodhead
11705 Boyette Road
Suite 171
Riverview, FL 33569

Dear Ms. Goodhead:

Please refer to your New Drug Application (NDA) dated February 27, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for potassium chloride oral solution, 20 mEq/15 mL and 40 mEq/15 mL.

During our review of the microbiology section of your submission we identified the following deficiencies:

> In the Antimicrobial Effectiveness Testing (AET) summary report provided, only the 20 mEq/15mL formulation was tested. The justification for not testing the 40 mEq/15 mL formulation in the AET was that the two formulations have the same pH range and that differences in the formulations, specifically the additional potassium chloride salt and reduced propylene glycol of the 40 mEq formulation, would have no effect on the preservatives. The difference in the propylene glycol concentrations in the two formulations is significant at 16% w/v in the 20 mEq/15 mL and 7% w/v for the 40 mEq/15 mL formulation. The justification that the propylene glycol has no effect on the preservative system is not acceptable. Though it was stated that the propylene glycol's function in the formulation is a co-solvent, it is a known preservative and the significantly lower concentration in the 40 mEq/15mL formulation may have an impact on the overall effectiveness of the preservative system; therefore, the 40 mEq/15 mL formulation should be tested in the AET.

We have the following proposed Postmarketing Commitment to address the above concern:

> Please perform the Antimicrobial Effectiveness Testing on the 40 mEq/15 mL formulation (as was done for the 20 mEq/ 15 mL formulation). At completion of the study, the complete report for the AET study should be submitted to the Agency as a CBE-0 supplement.

Please respond to this letter in writing. If you agree to conduct the requested testing, please propose a timeline for its completion and submission of the supplement.

If you have any questions, please call Russell Fortney, Regulatory Project Manager at (301) 796-1068.

Sincerely,

{See appended electronic signature page}

Olen Stephens, Ph.D.
Acting Branch Chief
Branch I, Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

OLEN M STEPHENS
10/22/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-DDMAC-RPM	Russell Fortney, RPM (301-796-1068) DCRP

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS
8/13/14		206814	(PLEASE CHECK OFF BELOW)

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Potassium chloride oral solution	Standard		Within 2 weeks of providing substantially complete labeling.

NAME OF FIRM:	
Pharma-Med, Inc.	PDUFA Date: December 27, 2014

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☒ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☒ ORIGINAL NDA/BLA
- ☐ IND
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☒ INITIAL PROPOSED LABELING
- ☐ LABELING REVISION

EDR link to submission: \\CDSESUB1\EVSPROD\NDA206814\206814.enx

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Wrap-Up Meeting: Not scheduled yet

SIGNATURE OF REQUESTER
Russell Fortney

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check all that apply)
	☐ eMAIL ☒ DARRTS ☐ HAND

06/18/2013

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

/s/

RUSSELL FORTNEY
08/13/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206814

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Pharma-Med, Inc.
Attention: Mr. Nebiyou Getahoun
President
941 Marcon Boulevard, Suite 301
Allentown, PA 18109

Dear Mr. Getahoun:

Please refer to your New Drug Application (NDA) dated February 27, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for potassium chloride oral solution, 20 mEq/15 mL and 40 mEq/15 mL.

We also refer to your amendments dated April 3 and 10, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Standard. Therefore, the user fee goal date is December 27, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by October 24, 2014.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. Please provide updated stability data for the drug product as soon as they are available.

2. Please provide a table comparing the formulation (components and composition) of your proposed drug product and formulations used in the PK references upon which you are relying. Please provide a justification for any difference between these formulations (proposed product

and the oral solution formulations used in the PK references) with respect to concentration, inactive ingredients, pH, and osmolality.

3. Please provide the report for the antimicrobial effectiveness testing.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, please call Russell Fortney, Regulatory Project Manager at (301) 796-1068.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

NORMAN L STOCKBRIDGE
04/25/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206814

NDA ACKNOWLEDGMENT

Pharma-Med, Inc.
Attention: Mr. Nebiyou Getahoun
President
941 Marcon Boulevard, Suite 301
Allentown, PA 18109

Dear Mr. Getahoun:

We have received your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Potassium Chloride Oral Solution, USP, 20 mEq/15 mL and 40 mEq per 15 mL (RX Only)

Date of Application: February 27, 2014

Date of Receipt: February 27, 2014

Our Reference Number: NDA 206814

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 28, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please contact:

Russell Fortney, R.Ph.
Regulatory Health Project Manager
(301) 796-106

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc: Melissa L. Goodhead, MSc, RAC, PPSI
US Agent for Pharma-Med, Inc.
11705 Boyette Road, Suite 171
Riverview, FL 33569

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

/s/

EDWARD J FROMM
03/19/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

P-IND (b) (4)

MEETING MINUTES

Lehigh Valley Technologies, Inc.
Attention: William Reightler
Vice President - Regulatory Affairs
514 North 12th Street
Allentown, PA 18102

Dear Mr. Reightler:

Please refer to your Pre-Investigational New Drug Application (PIND) for potassium chloride oral solution and powder for solution.

We also refer to the meeting between representatives of your firm and the FDA on June 20, 2012.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Russell Fortney, Regulatory Project Manager, at (301) 796-1068.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	P-IND Meeting
Meeting Date:	June 20, 2012
Meeting Location:	Teleconference
Application Number:	P-IND (b) (4)
Product Name:	Potassium chloride oral solution and powder for solution
Indication:	Treatment of hypokalemia
Sponsor/Applicant Name:	Lehigh Valley Technologies, Inc.
Meeting Chair:	Norman Stockbridge
Meeting Recorder:	Russell Fortney

FDA ATTENDEES

Division of Cardiovascular and Renal Products	
Norman Stockbridge, MD, PhD	Director
Aliza Thompson, MD	Medical Team Leader
Nancy Xu, MD	Medical Reviewer
Al DeFelice, PhD	Pharmacology Team Leader
Tom Papoian, PhD	Pharmacology Team Leader
Edward Fromm, RPh, RAC	Chief, Project Management Staff
Russell Fortney	Regulatory Project Manager
Office of Clinical Pharmacology	
Rajanikanth Madabushi, PhD	Team Leader
Sreedharan Sabarinath	Reviewer
Office of New Drug Quality Assessment	
Kasturi Srinivasachar, PhD	Chemistry Pharmaceutical Assessment Lead
Angelica Dorantes, PhD	Biopharmaceutics Team Leader
Houda Mahayni, PhD	Biopharmaceutics Reviewer
Office of Compliance	
Charles Lee, MD	Senior Medical Advisor
Office of New Drugs	
Sally Loewke, MD	Assistant Director for Guidance and Policy

LVT ATTENDEES

Jeff Moshal	Chief Executive Officer
William Reightler	Vice President of Regulatory Affairs
Michael Libman	Chief Operating Officer and VP of Technical Affairs
(b) (4)	

BACKGROUND

Oral potassium chloride is currently approved as a tablet in various formulations from various manufacturers. Additionally, liquid formulations are available, either as solutions or powders for solution, as marketed unapproved products. LVT is proposing to submit a 505(b)(2) New Drug Application for a potassium chloride oral solution and a potassium chloride powder for oral solution. The sponsor requested this meeting to reach agreement with the Agency on the requirements for such an application. Preliminary responses to the sponsor's submitted questions were communicated to the sponsor prior to the meeting and are copied below followed by any additional discussion that took place during the meeting.

DISCUSSION

The following questions were addressed:

Regulatory/Procedural

3.1 Question: Has the Agency previously established the safety and efficacy of Rx only immediate release Potassium Chloride products as described in CFR sec. 201.306 "Potassium salt preparations intended for oral ingestion by man"? This regulation includes products that contain 20 milligrams or more of Potassium per milliliter and solid dosage forms containing 100 mg or more of Potassium per dose.

Preliminary FDA response: The regulation set forth in 21 CFR 201.306 is a regulation addressing required labeling for potassium salt preparations for human oral ingestion. It does not establish the safety and efficacy of any potassium chloride product.

Additional discussion during meeting: No additional discussion.

3.2 Question: Does the Agency believe that it is appropriate to now require approval of all prescription oral dosage forms, including oral solution preparations and powder for reconstitution into oral solutions, of Potassium Chloride for the treatment and prevention of Hypokalemia?

Preliminary FDA response: FDA cannot commit in advance to a particular plan for enforcement action for any specific product. However, our Marketed Unapproved Drugs Compliance Policy Guide (CPG) lists the risk based enforcement priorities used by the Agency when determining whether to take an enforcement action against unapproved drugs. For additional information regarding the CPG, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070290.pdf

Additional discussion during meeting: The sponsor asked if the currently marketed oral potassium solution and powder products require an approved NDA. Dr. Lee responded that unless a product is (1) generally recognized as safe and effective and used for a material time and extent, (2) the subject of an applicable monograph, or (3) has been designated as grandfathered (none of which apply to the oral potassium products in question), all drug products require an approved NDA. These products are therefore considered to be unapproved new drugs.

3.3 Question: If a New Drug Application is submitted, should CFR 201.306 be used for the demonstration of Safety and Efficacy for a 505 (b)(2) New Drug Application for a 10% Oral Solution and 20 mEq Powder for Oral Solution dosage form of Potassium Chloride?

Preliminary FDA response: Please see response to Question 3.1. Please also refer to the response to Question 3.4 for information on which a sponsor may rely to support approval of an application submitted through the 505(b)(2) regulatory pathway.

Additional discussion during meeting: No additional discussion.

3.4 Question: Does the Division agree that the 505(b)(2) submission should use the clinical data, pharmacology data and references in the identified Reference Listed Drug to support the proposed products labeling, efficacy and safety?

Preliminary FDA response: The 505(b)(2) regulatory pathway permits an applicant to rely on the Agency's findings of safety and effectiveness for a listed (i.e., approved) drug(s). It appears that a 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate. We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature.

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which we consider to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that is the subject of an NDA approved under section 505(c) of the FD&C Act (in other words, an application approved under section 505(j) of the Act (i.e., ANDA, generic drug) may not be cited as a listed drug). The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you choose to rely on FDA's finding of safety and/or effectiveness for a listed drug(s) and you intend to use your proposed comparative clinical trial to establish a bridge between your proposed drug product and the specified listed drug(s), then you should use the specified listed drug(s) (rather than a bioequivalent ANDA product) as the comparator.

If you choose to rely on FDA's finding of safety and/or effectiveness for a discontinued listed drug(s) and intend to support the scientific appropriateness of reliance through a comparative bioavailability study, you should use the ANDA product designated as the RLD in the Orange Book as the comparator in a comparative clinical trial to establish a bridge between your proposed drug product and the specified listed drug(s). Note also that reliance on FDA's finding of safety and/or effectiveness for a discontinued listed drug(s) is contingent on FDA's finding that the drug was not discontinued for reasons of safety or effectiveness.

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a duplicate of that drug and eligible for approval under section 505(j) of the FD&C Act, we may refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

3.5 Question: If a New Drug Application is approved for 10% Oral Potassium Chloride Solution and 20 mEq Powder for Reconstitution into an Oral Solution for the treatment and prevention of Hypokalemia would the unapproved oral solution and powder forms of Potassium Chloride prescription products be removed from the market?

Preliminary FDA response: Please see response to Question 3.2 above.

Additional discussion during meeting: No additional discussion.

3.6 Question: If CFR 201.306 cannot be used for the demonstration of Safety and Efficacy for a 505 (b)(2) New Drug Application for a 10% Oral Solution and 20 mEq Powder for Oral Solution dosage form of Potassium Chloride and an *in vivo* clinical trial is required, will section (2 (b)) of CFR 201.306 for oral solutions be revised?

Preliminary FDA response: Please see response to Question 3.1.

Additional discussion during meeting: No additional discussion.

Clinical

3.7 Question: Based on the aqueous solubility of the active ingredient, route of administration, published bioavailability data comparing the two dosage forms, and previous determination by the Agency that the dosage forms are interchangeable for the intended use as codified per CFR sec. 201.306, the Sponsor intends to request that the FDA waive the requirement for *in vivo* bioavailability or bioequivalence per 21 CFR 320.22 (b) (3). Does the Agency agree with the request for waiver of the requirement for *in vivo* bioavailability or bioequivalence?

Preliminary FDA response: We have been unable to reach a consensus regarding questions 3.7 and 3.8. We will be prepared to discuss these questions during the meeting.

Additional discussion during meeting: Dr. Dorantes said that a biowaiver is feasible for the proposed products. The sponsor should include in their NDA submission a biowaiver request for these products and provide the following supportive information: 1) published literature supporting the bioequivalence between the RLD, Potassium chloride Extended Release Tablets and their proposed potassium chloride products, and 2) literature demonstrating that the excipients used in their products do not affect bioavailability. The sponsor asked if data using urinary excretion of potassium would be acceptable to support a biowaiver. Dr. Dorantes agreed that showing bioequivalence based on urinary excretion of potassium is acceptable.

3.8 Question: If an *in vivo* clinical trial is required, is the proposed clinical pharmacology study design sufficient to support a 505(b)(2) NDA filing for 10% Potassium Chloride Oral Solution and 20 mEq Powder for Reconstitution into an Oral Solution, and to establish the necessary "clinical bridge" to the Reference Listed Drug? If not, what additional studies would be required? The proposed study will be conducted using the Powder for Oral Solution and a bioequivalence waiver will be requested for the Oral Solution product. Is this acceptable to the Agency?

Preliminary FDA response: Please see our response to Question 3.7.

Additional discussion during meeting: See response to Question 3.7.

3.9 Question: Does the Division agree that this drug product qualifies for a waiver of the requirement to perform pediatric studies in all pediatric sub populations? If not, please comment.

Preliminary FDA response: We do not agree that your reasoning supports a waiver of the PREA requirements. However, we think it is possible to develop adequate instructions for use in pediatrics based on published literature. If that is the case, we think that it is likely that pediatric studies would not be required, though the final determination would be made by the Agency's Pediatric Review Committee after NDA submission.

Additional discussion during meeting: No additional discussion.

3.10 Question: If Lehigh Valley's product is not eligible for a waiver of pediatric studies, does the Division agree that pediatric studies can be deferred until after NDA approval?

Preliminary FDA response: Yes, we agree (see also our response to Question 3.9).

Additional discussion during meeting: No additional discussion.

Pharmacology/Toxicology

3.11 Question: As the requested indications for 10% Potassium Chloride Oral Solution and 20 mEq Powder for Reconstitution into an Oral Solution are consistent with the indications in CFR sec. 201.306 and NDA 019439 (Potassium Chloride Extended Release Tablet 20 mEq, Schering), the Sponsor proposes to perform no nonclinical studies prior to filing a 505(b)(2) NDA for the treatment of hypokalemia. If this proposal is not acceptable to the Division, what additional studies/data would be required?

Preliminary FDA response: This proposal is acceptable. Since the risk of GI mucosal injury is shared, to varying degrees, by all oral potassium salt formulations, do you have any insight, from published animal or human studies, on the mechanism of this toxicity that, occasionally, can be clinically important?

Additional discussion during meeting: No additional discussion.

Chemistry/Manufacturing/Controls

3.12 Question: It is LVT's intention to submit (b) (4) (b) (4) (b) (4) at the time of filing. The proposed expiration dating period at the time of filing will be 24 months.

Does the Division agree with the proposed CMC data package? If not, please comment.

Preliminary FDA response: No. You should submit a complete data package (i.e., 12 months of long term stability data in addition to 6 months of accelerated stability data) at the time of filing. An expiration dating period will be granted upon review of the submitted data in accordance with ICH Q1E.

Additional discussion during meeting: No additional discussion.

Additional Agency Comments

- (b) (4)

Additional discussion during meeting: No additional discussion.

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/s/

NORMAN L STOCKBRIDGE
07/19/2012