CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212832Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 130166

MEETING MINUTES

Fresenius Kabi USA, LLC
Attention: Brad Schmitt
Regulatory Affairs Manager
Three Corporate Drive
Lake Zurich, IL 60047

Dear Mr. Schmitt:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Potassium Phosphates Injection, USP.

We also refer to the teleconference between representatives of your firm and the FDA on May 31.2016. The purpose of the meeting was to review question 3 and 4 of the preliminary comments provided by the agency.

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

If you have any questions, call me at (240) 402-8689.

Sincerely,

{See appended electronic signature page}

Jacqueline LeeHoffman, Pharm.D.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Error Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Pre-IND

Meeting Date and Time: May 31, 2016 12:00 PM – 1:00 PM ET
Meeting Location: Teleconference

Application Number: 130166
Product Name: Potassium Phosphates Injection, USP
Indication: Hypophosphatemia (b) (4)
Sponsor/Applicant Name: **Fresenius Kabi USA, LLC**

Meeting Chair: Stephanie Omokaro, M.D.
Meeting Recorder: Jacqueline LeeHoffman, Pharm.D.

FDA ATTENDEES

Donna Griebel, M.D., Director, Division of Gastroenterology and Inborn Error Products (DGIEP)
Dragos Roman, M.D., Associate Director, DGIEP
Stephanie Omokaro, M.D., Clinical Team Leader, DGIEP
Wen-Yi Gao, M.D., Clinical Reviewer, DGIEP
Sushanta Chakder, Ph.D., Supervisor Pharmacologist/Toxicologist, DGIEP
Tracy Behrsing, Ph.D., Pharmacologist/Toxicologist, DGIEP
Yeh-Fong Chen, Ph.D., Team Leader, Statistical Reviewer, Division of Biometrics III (DBIII)
Min Min, Ph.D., Statistical Reviewer, DBIII
Kevin Bugin, M.S., RAC, Chief, Project Management Staff (Acting) , DGIEP
Danuta Gromek-Woods, Ph.D. Chemist, Office of Product Quality (OPQ)
David Lewis, Ph.D. Chemist, OPQ
Donna Snyder, M.D., Lead Medical Officer, Division of Pediatric and Maternal Health (DPMH)
Carolyn Yancey, M.D., Medical Officer, DPMH
Jeffrey Trunzo, Rph, MBA, Office of Unapproved Drug and Labeling Compliance OUDLC
Barbara Wise, Ph.D., RN, CPNP, Team Leader, OUDLC

SPONSOR ATTENDEES

Molly Rapp, V.P., Regulatory Affairs, US Innovation and Development, Generics and Standard Solutions

Ed Tabor, M.D., V.P., Regulatory Affairs, North America, Parenteral Nutrition, Colloids & Ketosteril
Maria Guseva, Pharm.D., M.S., Manager, Medical Affairs
Shweta Mowli, Project Manager
Brad Schmitt, Regulatory Affairs Manager

1.0 BACKGROUND

Fresenius Kabi USA, LLC currently markets Potassium Phosphates Injection, USP in three separate 3 mmol/mL presentations (Single Dose Vials of 5 mL, 15 mL and 50 mL). The drug product is indicated as source of phosphate, for addition to large volume intravenous fluids to prevent or correct hypophosphatemia in patients with restricted or no oral intake.

FDA sent Preliminary Comments to Fresenius Kabi USA, LLC on May 27, 2016.

2. DISCUSSION

The sponsor is seeking feedback and guidance from the Division on the proposed 505(b)(2) NDA submission on the following:

- To obtain the FDA's opinion and concurrence that the available peer-reviewed nonclinical literature adequately establishes the safety of Potassium Phosphates Injection, USP and that additional nonclinical studies are not required to support submission of a 505(b)(2) NDA for the indication of treatment of hypophosphatemia.
- To obtain the FDA's opinion and concurrence that available peer-reviewed literature and textbook medical literature supports the safe and effective use of Potassium Phosphates Injection, USP (b) (4) for the treatment of hypophosphatemia and that additional clinical studies are not necessary to support a 505(b)(2) NDA.

(b) (4)

- To obtain the FDA's opinion and concurrence that the proposed study consisting of a retrospective analysis of the hospital records of hypophosphatemia pediatric ICU patients treated with Potassium Phosphates Injection, USP is acceptable and would meet PREA requirements.
- To obtain the FDA's opinion and concurrence that Fresenius Kabi USA's Chemistry, Manufacturing and Control (CMC) dataset is sufficient to support a 505(B)(2) NDA.

2.1. NonClinical

Question 1:

Does the Agency concur that the nonclinical information available in the scientific literature

and summarized in this information package sufficiently establishes the safety of the drug product and that additional nonclinical studies are not required to support a 505(b)(2) NDA submission?

FDA Response to Question 1:

Yes, we agree that additional nonclinical studies are not needed to support a 505(b)(2) NDA submission for your proposed drug product.

Discussion:

No comment.

2.2. Clinical

Question 2:

Does the Agency concur that the clinical efficacy and safety data documented in the medical textbooks and medical literature and summarized in this information package is sufficient to support submission of a 505(b)(2) NDA for Potassium Phosphates Injection, USP for the treatment of hypophosphatemia (b) (4), without conducting additional clinical studies?

FDA Response to Question 2:

We agree that reliance on the published literature and FDA's finding of safety and effectiveness for sodium phosphate injection (NDA 018892) and potassium chloride injection (NDA 020161) is acceptable to support the submission of an NDA for potassium phosphate for the treatment of hypophosphatemia, if you provide adequate bridge to each listed drug.

Your proposed product does not contain the same active and inactive ingredients in the same concentration as the listed products. Therefore, a biowaiver cannot be granted. However, if you can provide scientific justification that potassium phosphate in the proposed product will undergo complete dissociation under physiological pH to liberate the potassium ion and phosphate ion in a physiological amount equivalent to what is liberated from the listed drugs (i.e., sodium phosphate and potassium chloride injection), based on 21 CFR 320.24(b)(6), the bridge between the listed drugs and the proposed drug product can be established. You will also need to provide the pH and osmolality of the final product to be injected/infused. You may submit a formal request for advice that includes your justification to support that an adequate bridge has been established for our review and we will determine whether additional *in vivo* relative bioavailability studies are needed for your drug product.

Provide your dosing rationale and justification to support the dose. It is premature to determine whether or not additional clinical studies will be required; this will be a review issue that will be based on the adequacy of the literature you submit.

Discussion:

No comment.

Question 3:

Does the Agency concur that a (b) (4) [redacted]

FDA Response to Question 3:

Your proposal of (b) (4) [redacted]

Discussion:

The sponsor asked about the open literature search for Sodium Phosphate Injection and Potassium Chloride injection to be acceptable for submission?

FDA responded that it is acceptable to bundle and submit the search to strengthen the reasoning for the submission.

Question 4:

For the purposes of meeting PREA requirements, does the Agency concur that the proposed study consisting of a retrospective analysis of the hospital records of hypophosphatemic pediatric ICU patients treated with Potassium Phosphates Injection is acceptable?

FDA Response to Question 4:

Retrospective analysis of pediatric hospital records may be submitted as supportive evidence; however, additional literature is likely needed to support pediatric use. Your specific proposal should be described in your iPSP.

Discussion:

The Agency has not made any determination on necessary pediatric studies, if the sponsor can support the iPSP with literature, please submit during the review.

2.3 Clinical Pharmacology

Question 5:

Does the Agency concur that the clinical Pharmacology data documented in the medical textbooks and medical literature and summarized in this information package are sufficient to support submission of a 505(b)(2) NDA for Potassium Phosphates Injection, USP without conducting additional pharmacokinetic or pharmacodynamics studies?

FDA Response to Question 5:

Please refer to our response for Question 2.

Discussion:

No comment.

2.4 Chemistry, Manufacturing and Controls

Question 6:

Does the Agency concur that manufacturing of one full scale commercial batch for each of the three presentations of the 3 mmol Potassium Phosphates Injection, USP packaged in 5 mL, 15 mL and 50 mL vials will be sufficient to support submission of a 505(b)(2) NDA for Potassium Phosphates Injection? Stability Data for each batch stored at 25 ± 2°C, 60 ± 4% RH through (b) (4) months and 40 ± 2°C, 75± 5% RH through (b) (4) months will be provided in the application to support a tentative expiration date of 24 months for the drug product stored at ambient conditions in each of the three presentations. Does the Agency agree that this data set should be sufficient to support a 505(b)(2) NDA with the proposed shelf-life of 24 months for the drug product?

FDA Response to Question 6:

Although we agree with your proposal of providing stability data for one full scale commercial batch for each presentation (5 mL, 15 mL, and 50 mL vials), submitting 6 months accelerated stability data along with (b) (4) months long term stability data will be insufficient to support the proposed 24 month expiration dating period.

At the time of the NDA submission, you will need to provide 6 months accelerated stability data and at least 12 months long term stability data for each batch of the 3 mmol Potassium Phosphates Injection, USP.

Please also be aware that you will need to follow the ICH Q3D guideline for elemental impurities qualifications in your drug product. Please also address the elements not included in ICH Q3D such as aluminum, (b) (4)

Discussion:

No comment.

ADDITIONAL COMMENTS REGARDING MARKETED UNAPPROVED DRUGS FROM THE OFFICE OF UNAPPROVED DRUGS AND LABELING COMPLIANCE (OUDLC)

The Agency is aware your firm currently markets Potassium Phosphates Injection, USP, an unapproved prescription drug product. The FDA encourages firms to voluntarily comply with the law by submitting applications for previously marketed unapproved prescription drugs. This process benefits public health by increasing assurance that marketed drugs are safe and effective for their intended uses as well as manufactured under current good manufacturing practices. When a company obtains approval of an NDA for products that other companies are marketing without approval, the FDA is more likely to consider compliance action. However, FDA considers several factors such as the effect on public health of removing the unapproved products from the market, the ability of the applicant holder to meet patient needs by adequately supplying the market, assuring that the components and finished drug products are manufactured under quality standards, and Agency resources. We encourage your firm to consider these important factors as the application progresses through the review process and to open discussions with the Drug Shortage Staff and the Office of Compliance if appropriate.

3.0 505(b)(2) REGULATORY PATHWAY

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)* (October 1999), 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 that had challenged 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, in part, 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, in part, 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 or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered 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 was approved in an NDA under section 505(c) of the FD&C Act. 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 propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

Reference ID: 4526176

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	***Nonclinical toxicology***
2. Example: NDA XXXXXX "TRADENAME"	***Previous finding of effectiveness for indication X***
3. Example: NDA YYYYYY "TRADENAME"	***Previous finding of safety for Carcinogenicity, labeling section XXX***

4.

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 a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to 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 Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

4.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*

Reference ID: 4526176

at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

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/s/

JACQUELINE D LEEHOFFMAN
06/09/2016