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RESEARCH**

APPLICATION NUMBER:

200656Orig1s000

OTHER ACTION LETTERS



NDA 200656

COMPLETE RESPONSE

APP Pharmaceuticals, LLC.
Attention: Aparna Dagar, Ph.D.
Supervisor Regulatory Affairs
1501 East Woodfield Road, Suite 300E
Schaumburg, Illinois 60173

Dear Dr. Dagar:

Please refer to your New Drug Application (NDA) dated January 28, 2011, received January 28, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Kabiven and Perikabiven (lipid injectable emulsion with amino acids and electrolytes and dextrose).

We acknowledge receipt of your amendments dated March 10, 2011, April 6, 2011, April 25, 2011, May 10, 2011, June 17, 2011, July, 7, 2011, July 27, 2011, August 5, 2011, August 19, 2011, September 2, 2011, September 7, 2011, September 16, 2011, October 13, 2011, and November 11, 2011.

We also acknowledge receipt of your amendments dated October 21, 2011 and November 18, 2011 which were not reviewed for this action. You may incorporate applicable sections of the amendments by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

1. Information to [REDACTED] (b) (4) is insufficient.

As communicated to you in our September 8, 2011 letter, you must submit:

- A. [REDACTED] (b) (4)

- B. [REDACTED] (b) (4)

(b) (4)

PRODUCT QUALITY

2. Information on the amount of heavy metals in each compartment of the three chamber bag and the total amount of heavy metals in each product is inadequate. The presence of heavy metals in these products may have significant adverse effects on organs and tissues such as nephropathy, neurotoxicity, and hepatotoxicity.

As communicated to you in our September 29, 2011 letter, you must provide:

- A. Data to show the levels of arsenic, cadmium, lead, mercury, chromium, copper, manganese, selenium, and zinc in each of the compartments for three batches of each product with the information reported as ppm. Batches selected for testing should not be successively manufactured batches; batches from ongoing stability studies are appropriate for this purpose. If multiple package sizes are manufactured from a common batch, data for only one package size should be reported. In addition, specify whether your products are being developed using molybdenum, nickel, palladium, platinum, vanadium, osmium, rhodium, ruthenium, or iridium, and if so, provide the above information for each of these metals as well.
 - B. An estimated quantity of each product administered over a 24-hour period.
3. Adequate controls for the levels of heavy metals specified in Item #2 in each of the compartments have not been provided. Due to the large volume to be infused into patients, develop specifications and adequate acceptance criteria to control the amount of daily intake of these heavy metals.
 4. You revised the proposed expiration dating period to (b) (4) months because you observed precipitation in your product when it is stored at the proposed storage conditions for longer than that time period.

As discussed in a teleconference on November 4, 2011, to support a (b) (4)-month expiration, provide data to demonstrate that product with higher levels of particulate matter, but still within specification, does not precipitate on in-use refrigerated storage. We will evaluate the results of these studies in your resubmission

5. DMF # (b) (4) has been reviewed in support of NDA 200656 and found to contain deficiencies. A letter dated August 31, 2011 was sent to the DMF holder listing the deficiencies. The DMF holder should address the deficiencies and update the DMF by directly submitting information to the DMF. You should notify us when the DMF holder has submitted the requested information.

6. Confirm that the (b) (4) meets (b) (4)

DEVICE PERFORMANCE

7. You performed a test to demonstrate the resistance of the (b) (4) packaging to temperature, pressure and leakage, however, it is unclear whether altitude was accounted for as part of testing regimen. We believe that it is more relevant to demonstrate the pressure at which the (b) (4) bag bursts. If the burst pressure significantly exceeds (for example, by a factor of 2) the typical atmospheric pressures expected with higher altitudes, then concerns of the bag bursting at these altitudes will have been mitigated.

You should repeat the testing regimen to determine burst pressure and utilize appropriate statistical methods to determine sample size and to interpret the test results.

8. (b) (4)

9. You performed a test to demonstrate that the injection point does not leak when it is punctured by a 23 gauge needle. It appears that the septum at the injection point was punctured only once before subjecting the bag to 20 kPa pressure. However, from the device description provided, it appears that one of the points is utilized to spike the bag with medication after the contents are mixed. It is conceivable that this septum would be penetrated multiple times prior to beginning the infusion. Also, it is unclear whether the 23 gauge needle will adequately test the non-coring nature of the septum at the injection point.

Therefore, you should:

- A. Clarify whether the injection point could be penetrated multiple times, and if so, modify the test to account for multiple punctures, prior to testing the bag for leakage.
- B. Test the injection point leakage after the septum is punctured with a 19 or 21 gauge needle, needle gauges that are more representative of an extreme needle size for penetrating the injection point septum.

HUMAN FACTORS ASSESSMENT

10. Although the (b) (4) bag will be utilized by health care providers, after evaluating the packaging sample provided, we found it very cumbersome to manipulate. Therefore, to ensure that use-related hazards associated with using the (b) (4) bag have been successfully identified and mitigated, you should perform an assessment to identify potential use-related hazards are no different than the usual hazards that clinicians face when delivering drug product through other IV bags. Based on this assessment, you can then determine what human factors studies should be conducted, as outlined in CDRH's *Guidance for Industry and FDA Premarket and Design Control Reviewers, Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*. This guidance may be found at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094461.pdf>.

When performing this testing, consideration should be given to the following:

A. Devices and Labeling Used and Training

The (b) (4) bags used in human factors studies should represent the final design, and include instructions for use or any other labeling materials.

The training provided to study participants should approximate the training that actual end users will receive. Describe the training you plan to provide in your studies and how it corresponds to realistic training levels.

Participants should assess the clarity of the instructions for use and you should assess the extent to which the instructions support safe and effective use of the (b) (4) bag.

Study results demonstrating effectiveness of the training and instructions for use should be analyzed separately from the results of user performance.

B. User Tasks

The rationale for which user tasks will be included should be provided, and how many trials each participant would complete to adequately assess user performance. The tasks should be prioritized to reflect the relative magnitude and severity of the potential impact of inadequate task performance on the safety of the device and the user.

C. Use Environment and Conditions

Human factors studies should be conducted in an environment that includes or simulates all key aspects of the real-world environments in which you anticipate your device would be used.

Identification of potentially challenging use conditions (e.g., use with gloves or wet fingers, dim lighting, noisy situations, etc.) should be anticipated, and use of the bags under such conditions should be evaluated.

Describe the testing environment and realism of the simulated use in sufficient detail and justify how they were appropriate for testing the device.

D. Study Participants

For devices that are intended to be marketed in the U.S., human factors studies should be conducted in the U.S. with (American) English speaking participants. A minimum of 15 participants from each major user group should be tested. Participants should be representative of the intended end-user populations. If users with distinctly different characteristics (e.g., skill sets or experience levels) will use the bags, you should include 15 from each distinct group.

A rationale that supports that these groups are representative of the overall population of users for the device should be provided. Participants should not be your own employees, or those that have been exposed to the products prior to the testing.

E. Data Collection

Data collected and analyzed in human factors studies should be described in terms of how they support the claim that the device can be used safely and effectively by the indicated users. Both empirical and qualitative data will be needed.

Empirical Data. Participants should be given an opportunity to use the device independently and in as realistic a manner as possible, without guidance, coaching, praise, or critique from the test facilitator/moderator. Data regarding the successful or failed performance of key tasks should be measured directly rather than by soliciting participant opinions. Observing participant behavior during the study will also permit assessment of participants' adherence to protocol and proper technique, and of any errors or problems that occur.

Qualitative Data. At the conclusion of the study, participants should be asked open-ended questions such as, "Did you have any difficulty using this device? If so, can you tell me about that?" The questions should explore performance of each critical task involved in the use of the device and any problems encountered. Since the labeling and instructions for use are considered part of the user interface for the device, the questions should cover those components as well.

The analysis of performance and subjective data should be directed toward understanding user performance and, particularly, task failures. The analysis should determine the nature of failures, the causes of failures, and the clinical impact. Every participant who experiences a "failure" (does something that would have led to harm under actual

conditions of use), should be interviewed about that failure to determine the cause of the failure from the perspective of the participant.

F. Protocol

You are encouraged to submit human factors study protocols for review by staff in the Center for Devices and Radiologic Health to ensure that the study(ies) are aligned with published guidance.

LABELING

11. Submit revised content of labeling and draft container labels that incorporate the proprietary name, Perikabiven, and the established name, lipid injectable emulsion with amino acids and electrolytes and dextrose.

Your response must include updated 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>.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

FACILITY INSPECTIONS

During recent inspections of the manufacturing facilities for this application, our field investigator conveyed deficiencies to the representatives of some facilities. Satisfactory resolution of these deficiencies is required before this application may be approved.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
 4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
 5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
 6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
 7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
 8. Provide English translations of current approved foreign labeling not previously submitted.

PROPRIETARY NAME

We refer to your correspondence, dated September 7, 2011, received September 8, 2011 requesting review of your proposed proprietary names, Kabiven (for central vein administration) and Perikabiven (for central and peripheral vein administration). We have completed our review of the proposed proprietary names and have concluded that the names are acceptable.

The proposed proprietary names, Kabiven and Perikabiven, will need to be re-reviewed upon resubmission of your NDA and 90 days prior to approval of your NDA. If we find the names unacceptable following the re-review, we will notify you. You should submit a letter in your resubmission stating you want us to review your names and provide us with the most current full set of labels.

If **any** of the proposed product characteristics as stated in your September 8, 2011 submission are altered prior to approval of the marketing application, the proprietary names should be resubmitted for review.

OTHER

We note that you identified Aminosyn II with Electrolytes in Dextrose with Calcium (NDA 019683) and Novamine 11.4% Injection (NDA 017957) as listed drugs relied upon for approval of your application and that these listed drugs have been discontinued. We will need to

determine that these listed drugs were not withdrawn from sale for reasons of safety and/or effectiveness prior to approval of your application.

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Maria R. Walsh, Associate Director for Regulatory Affairs, at (301) 796-1017.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
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/

JULIE G BEITZ
11/21/2011