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RESEARCH**

*APPLICATION NUMBER:*

**204767Orig1s000**

**OTHER ACTION LETTERS**



NDA 204767

**COMPLETE RESPONSE**

Fresenius Kabi USA, LLC  
Three Corporate Drive  
Lake Zurich, IL 60047

Attention: Aditi Dron  
Manager, Regulatory Affairs

Dear Ms. Dron:

Please refer to your September 28, 2012, New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Acetaminophen Injection, 10 mg/mL.

We acknowledge receipt of your amendments dated December 12 and 27, 2012, and February 4 and 22, March 13, 22, and 29, April 17 and 26, May 7 and 16, and June 13, 2013.

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.

**NONCLINICAL**

1. You have not provided adequate safety justification for the levels of (b) (4) leachables from the container closure system. To resolve this deficiency:
  - a. Submit the results of the proposed 4-week IV toxicology study of (b) (4) and a revised toxicological risk assessment.
  - b. Conduct and submit the results of a 4-week IV toxicology study of (b) (4) and a revised toxicological risk assessment for this compound. Alternatively, provide adequate data to support your conclusion that (b) (4) is virtually instantaneous in vivo such that exposure to the parent compound, when the product is used as directed, does not occur.

**PRODUCT QUALITY**

2. The leachable study data that you have submitted, 6 months at three different storage conditions and 12 months at one storage condition (b) (4) fill volume, are inadequate to support the safety of your drug product. To resolve this deficiency, submit additional leachable data at 18-month and 24-month time points for all

stability batches at long-term storage conditions for the 100 mL fill volume of the freeFlex <sup>(b)(4)</sup> container closure system.

3. Your application referenced the Master File (MF) 26696. This MF was found to be inadequate to support your submission and a deficiency letter was sent to the MF holder on June 24, 2013. These deficiencies must be adequately addressed before this application can be approved. As part of your response to this letter, include the date the MF holder amended their MF to address the deficiencies.

### **LABELING**

4. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, 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>.

### **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.

### **ADDITIONAL COMMENTS**

We have the following comments/recommendations that are not approvability issues:

1. Once you have evaluated the levels of leachables in the drug product over the course of the entire intended shelf-life, you must submit revised toxicological risk assessments based on the worst-case exposures. Final determination of the adequacy of your leachables safety assessment can only be provided upon review of the definitive stability data.
2. You have proposed to complete in vitro bacterial reverse mutation studies (Ames tests) for both [REDACTED] (b)(4). The final reports for these studies are not required for approval. However, when the studies have been completed, the results should be submitted to the NDA.

Additionally, the listed drug upon which your application relies is subject to a period of patent protection and therefore final approval of your application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be made effective until the period has expired.

### **OTHER**

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 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 Diana L. Walker, Ph.D., Sr. Regulatory Health Project Manager, at (301) 796-4029.

Sincerely,

*{See appended electronic signature page}*

Sharon H. Hertz, M.D.  
Deputy Director  
Division of Anesthesia, Analgesia, and  
Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SHARON H HERTZ  
07/25/2013