

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**212156Orig1s000**

**OTHER ACTION LETTERS**



NDA 212156

**COMPLETE RESPONSE**

Par Sterile Products, LLC  
Attention: Carla English  
Associate Director, Regulatory Affairs  
Six Ram Ridge Road  
Chestnut Ridge, NY 10977

Dear Ms. English:

Please refer to your new drug application (NDA) dated July 18, 2019, received July 18, 2019, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Micafungin for Injection, 50 mg/vial and 100 mg/vial.

We also acknowledge receipt of your amendment dated April 6, 2020, which was not reviewed for this action. You may incorporate applicable sections of the amendment 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.

**PRODUCT QUALITY**

1. Regarding the compatibility studies in your Pharmaceutical Development Report, we note the assay values are (b) (4) mg/mL at time (b) (4) and (b) (4) mg/mL at (b) (4) hours for the 5% dextrose diluted admixture of 100 mg drug product as shown in Table 7-4 on page 126 of 134. The assay value of (b) (4) mg/mL is more than (b) (4) % off from the target 0.5 mg/mL concentration and this could affect the efficacy of the drug product. Conduct a root cause analysis to determine the reason for the low assay value. After determining the cause and correcting, reconduct the assay test of the in-use-stability study to support labeling.
2. Regarding the drug product specification:
  - a. The proposed acceptance criterion for Impurity (b) (4) is NMT (b) (4) %. Tighten the limit to NMT 0.2% per ICH Q3B or provide toxicology data to justify the limit.
  - b. The proposed acceptance criterion for specified impurity at (b) (4) is NMT (b) (4) %. The limit is above the qualification threshold. Justify the limit with toxicology data. Alternatively, tighten the limit to NMT 0.2% per ICH Q3B.

- c. The limit NMT (b) (4) % for any unspecified impurity is above the qualification threshold. Tighten the limit per ICH Q3B.

## **NONCLINICAL**

1. Provide your revised leachables assessment, including the toxicological assessment you planned to provide for (b) (4) on July 31, 2020. The adequacy of your revised leachables study will be assessed at time of resubmission.
2. As noted in the product quality comments above, the proposed acceptance criterion for Impurity (b) (4) (NMT (b) (4) %), impurity at (b) (4) (NMT (b) (4) %) and any unspecified impurity (NMT (b) (4) %) are above the ICH Q3B qualification thresholds of NMT 0.2%. If the acceptance criterion cannot be tightened to NMT 0.2%, provide adequate characterization for impurity at (b) (4) and any unspecified impurity(ies), along with a comprehensive toxicological assessment for all impurities greater than 0.2% when administered intravenously. If sufficient toxicity information is not available, additional nonclinical studies may be recommended to qualify the safety of impurities > 0.2%.

Please refer to ICH Q3B(R1): Impurities in New Drug Products (available at <https://www.fda.gov/media/71733/download>) and ICH M7(R1): Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk (available at <https://www.fda.gov/media/85885/download>) for additional information on the qualification of impurities in drug products.

## **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. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information<sup>1</sup> and Pregnancy and Lactation Labeling Final Rule<sup>2</sup> websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential

<sup>1</sup> <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>

<sup>2</sup> <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>

- 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 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Submit draft labeling that addresses our proposed revisions in the attached labeling.

Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.<sup>3</sup>

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

### **CARTON AND CONTAINER LABELING**

Submit revised draft carton and container labeling based on our proposed revisions dated March 30 and April 9, 2020, as agreed to in your submissions of April 6 and 10, 2020.

### **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 in the original submission.

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<sup>3</sup> <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

- Present tabulations of the new safety data combined with the original application data.
  - Include tables that compare frequencies of adverse events in the original application 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 application 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.

## **FACILITY INSPECTIONS**

An inspection of the [REDACTED] (b) (4) facility is required before the application can be approved as the FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP. Due to U.S. Government and/or Agency-wide restrictions on travel, we were unable to conduct an inspection during the current review cycle for your application. You may respond to the other deficiencies in this Complete Response letter while the travel restrictions remain in effect. However, even if all other deficiencies are addressed, the application cannot be approved until the required FDA inspection is conducted and the findings are assessed with regard to your application.

### **ADDITIONAL COMMENTS**

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

1. We note that (b) (4) for the drug substance in the drug product composition. Provide additional justification (b) (4) We recommend that you provide experimental data (b) (4)

(b) (4)

Provide the experimental results (b) (4) and corresponding assays in tabular format.

2. Regarding the compatibility studies in your Pharmaceutical Development Report, it appears that Table 7-3 and Table 7-4 are the same. Comment on why the extra table is listed.

3. Regarding the assay method for Micafungin Sodium in Drug Product:

(b) (4)

4. With respect to your response to Deficiency #2 and the related substance method (MET-00698) dated November 22, 2019:

(b) (4)

(b) (4)

5. We note that in your amendment dated February 12, 2020, the structure for Micafungin Impurity (b) (4) has been corrected in Section 3.2.S.3.2, but not in Section 3.2.P.5.5. Update Section 3.2.P.5.5 accordingly for Micafungin Impurity (b) (4).

### **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 in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference 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 draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

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 Eva Zuffova, MS, PhD, Regulatory Project Manager, at (301) 796-0697.

Sincerely,

*{See appended electronic signature page}*

Sumathi Nambiar, MD, MPH  
Director  
Division of Anti-Infectives  
Office of Infectious Diseases  
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Labeling

29 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page



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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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SUMATHI NAMBIAR  
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