CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212156Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 212156

REFUSAL TO FILE

Par Sterile Products, LLC
Attention: Michael Niebo
Director, Regulatory Affairs
Six Ram Ridge Road
Chestnut Ridge, NY 10977

Dear Mr. Niebo:

Please refer to your New Drug Application (NDA) dated November 19, 2018, received November 19, 2018, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Micafungin for Injection, 50 mg/vial and 100 mg/vial.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reason:

Chemistry, Manufacturing and Controls

In order to assure a suitable retest date for the drug substance and expiration date for the drug product, the Agency expects that applicants meet the provisions of ICH Q1A (R2) and provide at least 12 months of long-term stability data for at least three primary stability batches for both the drug substance and the drug product at the time of NDA submission. The FDA may make exceptions to this minimum stability data package in the case of certain applications. These type of exceptions, per the tenets of the PDUFA "commitment letter", are agreed upon at a pre-NDA meeting. Furthermore, per the PDUFA "commitment letter", if no agreement exists between the FDA and the applicant on the contents of a complete application or delayed submission of certain components of the application, the applicant's submission is expected to be complete at the time of original submission. The "commitment letter" further notes that incomplete applications, including applications with components that are not received within 30 calendar days after receipt of the original submission, will be subject to a Refuse-to-File decision.

We acknowledge the December 13, 2018, amendment to the NDA, which requested a (b) (4) expiry for the drug product. However, the Agency had not agreed to accept a product with only (b) (4) months of stability data. Your letter dated November 19, 2018, stated "Par commits to provide the Agency with the final results of its ongoing stability testing studies (including 12-month data) as soon as such data is available." However, the Agency had not previously agreed to accept additional stability data after the NDA submission. If you resubmit the application, include the results of 12-month long-term stability data.

While not related to our refusal to file this application, you should address the following issues if the application is resubmitted:

Chemistry, Manufacturing and Controls

1. DMF (b) (4) is currently deficient. We expect that you work with the DMF holder to resolve all deficiencies prior to resubmitting the NDA.

2. We acknowledge that the leachables protocol and the simulation study results were provided; however, the results of the leachables study of the drug product in the proposed commercial container closure system should be submitted in the NDA. Provide results of one-time extractable and leachable studies for the proposed container closure system using screening analytical methods (such as HPLC, GC, etc.). The leachables study should test at least one drug product stability batch through expiry. The leachables study should include the proposed diluents to be used as reconstitution agents and the duration of this study should be equivalent to the in-use period of the drug product. Place the constituted solutions in an inverted position for the leachables study. Refer to USP <1663> and <1664> for the assessment of leachables in the drug product from the container closure system.

Pharmacology/Toxicology

1. Your resubmission should include a comprehensive summary of the nonclinical pharmacology and toxicology information for micafungin in Module 4, including a review and summary of the published literature on nonclinical safety information for micafungin. In your resubmission, you should clearly identify the nonclinical pharmacology and toxicology 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. We remind you that 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.

2. In accordance with current FDA best practices and recommendations by the Product Quality Research Institute workgroup on parental products, you will need to submit a comprehensive toxicological risk assessment (i.e., local toxicity, systemic toxicity, mutagenicity, carcinogenicity, reproductive toxicity, etc.) for any leachable and extractable that exceeds a daily total intake limit of 5 mcg/day. From a genetic toxicology perspective, any leachable that contains a structural alert for mutagenicity must not exceed 20 mcg/day for an indication of > 1 to 12 months for most potentially genotoxic impurities or be adequately qualified for mutagenicity and carcinogenicity as described in ICH Guidance M7(R1). The overall risk assessment should be based on the maximum level of each leachable and extractable detected in long-term stability samples that include any intended secondary container closure system(s) unless otherwise justified. Leachable and extractable testing should be conducted on at least one drug product registration stability batch and be continued until the planned expiration date is reached. Absence of adequate information to support the safety of identified leachables

and extractables at the levels detected in your drug product may require additional nonclinical qualification studies. Refer to ICH Guidance M7(R1) "Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk" and ICH Guidance Q3B(R2) "Impurities in New Drug Products" for additional information on the safety qualification of impurities.

Labeling

1. Your prescribing information (PI) is not compliant with the Pregnancy and Lactation Labeling Rule (PLLR) content and format requirements [see Content and Format of labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014), codified at 21 CFR 201.56 and 201.57(c)(9)]. In your resubmission of the NDA, include draft labeling in PLLR format with updated data (e.g. available published literature) to support your proposed PLLR labeling.

   Information about the PLLR labeling requirements, including the types of data that should be submitted to support your proposed PLLR labeling, is available at: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm425398.pdf.

   Additional information about PLR labeling requirements including the Physician Labeling Rule, regulations, guidances, and other labeling resources is available at: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

Please note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review.

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee. If you choose to file over protest, FDA will generally not review any amendments to the application and will generally not issue information requests during the review cycle. Resubmission goals will not apply to any resubmission of this application.

PROPOSED PROPRIETARY NAME

If you intend to have a proprietary name for the above-referenced product, submit a new request for review of a proposed proprietary name when you resubmit the application. For questions regarding proprietary name review requests, please contact the OSE Project Management Staff via telephone at 301-796-3414 or via email at OSECONSULTS@cder.fda.gov.

If you have any questions, call Eva Zuffova, PhD, Regulatory Health Project Manager, at (301) 796-0697.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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.

/s/

SUMATHI NAMBIAR
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