

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761075Orig1s000

OTHER ACTION LETTERS



BLA 761075

COMPLETE RESPONSE

Mylan GmbH
c/o Mylan Pharmaceuticals Inc.
Attention: Barbara Militzer
Director, Regulatory Sciences, Biologics
781 Chestnut Ridge Road
PO Box 4310
Morgantown, WV 26504-4310

Dear Ms. Militzer:

Please refer to your Biologics License Application (BLA) dated December 9, 2016, received December 9, 2016, and your amendments, submitted under section 351(k) of the Public Health Service Act for MYL-1401H.

We also acknowledge receipt of your amendments dated September 29, and October 5, 2017, 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.

FACILITY INSPECTIONS

During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

PRODUCT QUALITY

(b) (4)

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

CARTON AND CONTAINER LABELING

We reserve comment on the proposed container label and carton labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated, March 29, 2017, which addresses the proposed proprietary name, Fulphila. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies of the product under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile and their relevance, if any, to whether there may be clinically meaningful differences between the proposed biosimilar product and the U.S.-licensed reference product.
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 clinical studies for the proposed indication using the same format as the original BLA submission.
 - Present tabulations of the new safety data combined with the original BLA data.
 - Include tables that compare frequencies of adverse events in the original BLA with the retabulated frequencies described in the bullet above.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study 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 BLA data.
6. Provide updated exposure information for the clinical studies (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this product, including adverse events known to be associated with the use of the product and immunogenicity. Include an updated estimate of use for this product 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:

Drug Substance – Microbiology and Product Quality

1. Only one batch of bulk drug substance (DE-B14-03-000018) was used to qualify the bioburden test. Conduct the qualification of the (b) (4) bioburden test for the bulk drug substance using two additional batches.
2. Perform an extractables and leachables study and a safety risk assessment for the (b) (4) used as a component of the drug substance container closure system to confirm low risk of leachables and low safety risk.

Drug Product – Microbiology



(b) (4)

5. Clarify the container closure integrity test conditions used during shipping validation and justify the use of a (b) (4) µm positive control. In addition, indicate the test acceptance criteria in mg/L of dye solution.
6. The endotoxin recovery studies included in amendment 0022 did not include quantitative recovery data. Repeat the study using different dilutions of the product in order to determine the endotoxin recovery in each sample.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b). 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 601.3(c). 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 FDA Guidance for Industry, "Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants," November 2015 at <https://www.fda.gov/downloads/drugs/guidances/ucm345649.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, contact Katie Chon, Regulatory Project Manager at katie.chon@fda.hhs.gov or (240) 402-6578.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Supervisory Associate Division Director
Division of Hematology Products
Office of Hematology and Oncology Products
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/

ALBERT B DEISSEROTH
10/06/2017