CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761166Orig1s000

OTHER ACTION LETTERS

BLA 761166

COMPLETE RESPONSE

PharmaEssentia Corporation
Attention: Craig Zimmerman, PhD
Vice President Medical and Drug Development
35 Corporate Drive, Suite 325
Burlington, MA 01803

Dear Dr. Zimmerman:

Please refer to your biologics license application (BLA) dated and received March 13, 2020, under section 351(a) of the Public Health Service Act for P1101.

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.

HUMAN FACTORS

Based on the results of the human factors (HF) validation study data, root cause analysis, and participants' subjective feedback, the proposed product design and user interface do not support safe and effective use of the product, as previously communicated to you in our October 15, 2020, correspondence regarding our review of your HF study results report. We recommend that you implement our HF protocol recommendations stated in the HF validation study protocol advice letter dated February 26, 2021, prior to commencing your HF validation study, consider additional design modifications and labeling changes, and submit the results of another HF validation study to demonstrate that the product can be used safely and effectively.

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[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected

[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

PROPRIETARY NAME

Please refer to correspondence dated, June 9, 2020, which addresses the proposed proprietary name, Besremi. 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.

FACILITY INSPECTIONS

Inspections of PharmaEssentia Corporation, FEI 2000012832, Taichung, Taiwan and PharmaEssentia Corporation, FEI 3005182038, Taipei, Taiwan are required before this application can be approved. FDA must assess the ability of these facilities to conduct the listed manufacturing operations in compliance with CGMP. Due to restrictions on travel, we were unable to conduct an inspection during the current review cycle for your application. You may respond to deficiencies in this Complete Response Letter while the travel restrictions remain in effect. However, even if these deficiencies are addressed, the application cannot be approved until the required FDA inspections are conducted and any findings are assessed with regard to your application. We will continue to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors.

For more information, please see the FDA guidances related to COVID 19.[3]

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d). The safety update should include data from all nonclinical and clinical studies/trials 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.

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.

[3] https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders

- 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 product. Include an updated estimate of use for 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:

1. Two batches of drug product were used to determine the suitability of the in-process bioburden test method conducted by (b) (4) However, three batches should be used for testing method suitability in the bacteriostasis/fungistasis assay. Therefore, provide in-process bioburden test method suitability results from one additional batch of P1101, 500 mcg/mL tested at (b) (4)

2. One batch of drug product was used to determine the suitability of the sterility test method conducted by PharmaEssentia Corporation. However, three batches should be used for testing method suitability in the bacteriostasis/fungistasis assay. Therefore, provide sterility test method suitability results from two additional batches of P1101, 500 mcg/mL tested at PharmaEssentia Corporation.

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 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 Carleveva Thompson, Regulatory Project Manager, at 301-796-1403.

Sincerely,

{See appended electronic signature page}

Ellis Unger, MD
Director
Office of Cardiology, Hematology, Endocrinology, and Nephrology
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/

ELLIS F UNGER
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