

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761085Orig1s000

OTHER ACTION LETTERS



BLA 761085

COMPLETE RESPONSE

Evolus, Inc.
Attention: Adelbert Stagg, PhD
Vice President Regulatory
1027 Garden Street
Santa Barbara, CA 93101

Dear Dr. Stagg:

Please refer to your Biologics License Application (BLA) dated and received May 15, 2017, and your amendments, submitted under section 351(a) of the Public Health Service Act for botulinum toxin Type A injection.

We also acknowledge receipt of your amendments dated March 16, March 30, April 10, and May 2, 2018, which were not reviewed for this action. You may incorporate applicable sections of these amendments 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

General

1. We received unsolicited information in various amendments that you submitted during the BLA review cycle. We have not fully determined the extent of the unsolicited changes made to the BLA at this time. Examples of these changes include i) process validation data from three new drug product (DP) lots manufactured with an updated commercial DP manufacturing process in an amendment received on December 15, 2017, and ii) changes to the DP post approval stability protocol to eliminate testing time points in an amendment received on December 1, 2017. To facilitate assessment of the impact of the changes made to the BLA on the approvability of your BLA, provide a list of all the unsolicited information and changes added to the BLA after the initial BLA receipt on May 15, 2017.

Microbiology: Drug Substance

2. The *Clostridium botulinum* culture purity (b) (4)
(b) (4)
(b) (4)
(b) (4). Provide the (b) (4) bacterial purity data from three batches. In addition, provide the (b) (4) limit and a description of the new test method.
3. You did not provide data to demonstrate that the DWP-450 drug substance (DS) is free of *Clostridium botulinum* spores. Provide spore monitoring data (b) (4)
(b) (4)
4. You provided insufficient data to demonstrate that DWP-450 DS is free of *Clostridium botulinum* vegetative cells. Provide monitoring data of *Clostridium botulinum* (b) (4)
(b) (4)
5. You provided no in-process bioburden and endotoxin data to demonstrate adequate microbial control of the DWP-450 DS (b) (4). Provide bioburden data (b) (4)
(b) (4). In addition, provide the qualification data for the bioburden and endotoxin test methods (b) (4). Furthermore, establish and provide in-process limits for these bioburden and endotoxin samples.
6. You provided no bioburden and endotoxin data (b) (4) to demonstrate adequate microbial control (b) (4). Provide microbiology validation data at commercial scale to demonstrate effective microbial control (b) (4)
(b) (4).
7. You provided no microbiology validation data (b) (4) of the DWP450 DS (b) (4) to ensure adequate microbial control (b) (4). Provide microbiology validation data (b) (4).

8. You did not establish endotoxin limits for the DWP450 DS (b) (4). Establish and provide endotoxin limits for the DWP450 DS (b) (4).
9. The current test volume for DS total aerobic microbial count (TAMC) is low and thus, the bioburden release test may not have sufficient sensitivity. (b) (4)
(b) (4) Provide bioburden qualification data of the DS (b) (4) and DS bioburden release data from three lots. Update the BLA with a description of the test method and the new DS bioburden specification.

Microbiology: Drug Product

10. You performed validation (b) (4) using (b) (4) the DWP-450 DP vials. No information was provided to assess (b) (4). Demonstrate that (b) (4) DWP-450 commercial DP vials (b) (4) effectively reduces endotoxin by a minimum of 3 logs and provide summary data and the validation report in the BLA resubmission.
11. You did not perform validation of the worst-case (b) (4) parameters on the DWP-450 DP vials to ensure that commercial vials are sealed appropriately and that container closure is integral. The vials used in the commercial manufacture of DWP-450 DP were not used to validate the (b) (4) process. In addition, worst-case (b) (4) parameters were not used during validation. Submit container closure integrity data to support the proposed parameters in the BLA resubmission.
12. You performed the (b) (4) validation study with (b) (4) the DWP-450 DP vials. No information was provided to assess (b) (4). Demonstrate that (b) (4) DWP-450 DP vials is effective (b) (4) and provide summary data and the validation report in the BLA resubmission.
13. The maximum sterile hold of (b) (4) for DWP-450 DP is not supported (b) (4). Provide data (b) (4) to support the sterile hold of (b) (4) for DWP-450 DP (b) (4). Include a summary of the (b) (4) environmental monitoring data in the BLA resubmission.
14. You did not demonstrate that the container closure integrity test detects breaches that may allow for bacterial ingress. You did not include positive controls in the method validation. Submit information to demonstrate that the container closure integrity testing can detect breaches \leq (b) (4) and include positive controls during routine testing.
15. You did not perform low endotoxin recovery testing of DWP-450 DP to assess whether the bacterial endotoxin test method can consistently detect endotoxin in the drug product. Certain product formulations have been reported to mask the detectability of endotoxin in

the USP <85> *Bacterial Endotoxin Test* (BET). Evaluate the effect of hold time on endotoxin detection by spiking a known amount of standard endotoxin (RSE or purified CSE) into undiluted DP and test for recoverable endotoxin over time (b) (4). Submit the report in the BLA resubmission.

16. You did not routinely monitor bioburden (b) (4) to verify continued microbial control of the drug product (b) (4). Implement routine bioburden monitoring (b) (4). In addition, provide a description of the bioburden test method and provide method qualification, summary data, and the qualification report.

Product Quality: Drug Substance and Drug Product

17. Reference materials play a critical role in confirming the suitability of analytical tests and the quality of the product during release and stability testing. The information you provided in the BLA suggests that your DS reference material management program does not generate sufficient quantities of a given reference material lot to support all the required testing. Revise your reference material qualification procedures to ensure that you generate sufficient quantities of reference material to support all the necessary testing, including qualification of future reference materials. In addition, revise the DS reference material qualification and requalification protocol to include adequate stability monitoring of the reference materials.
18. In your December 1, 2017 response to the November 13, 2017 information request to update the DP stability testing protocols to include DP reconstitution time, it appears that additional changes were made to the post-approval stability protocol originally submitted in the BLA to remove the testing points at 3, 6, 9, and 18 months. You did not provide sufficient stability data to support a reduced stability testing program. Therefore, the updated annual post-approval stability protocol in section 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment (Table 3.2.P.8.2-2) received on December 1, 2017 is not adequate to ensure that potential changes to commercial DP during storage are detected in a timely manner. Revise your annual stability protocol to include testing at 3, 6, 9, and 18 months as recommended by ICH Q5C guidelines.
19. In your March 9, 2018 response to the March 2, 2018 information request to describe Evolus' role in DWP-450 lot release, you stated that some of Evolus' quality responsibilities will be delegated via quality agreements and standard operating procedures (SOPs) to your "soon to be established distributor". Your response indicates that the distributor may be responsible for: visual inspection for shipping or water damage; verification of release certifications (Certificate of Analysis) from Daewoong Pharmaceuticals Co., Ltd.; verification of shipment quantity and lots numbers; and verification that appropriate temperature was maintained during shipment. You also state that you will rely on the distributor's SOPs and Quality Assurance unit for these activities. If your distributor is responsible for performing release operations for Evolus then they appear to fit the definition of a manufacturer rather than a distributor per 21

CFR 600.3 (t), (u), and (aa) and should be listed as a manufacturer in the license application.

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>

PROPRIETARY NAME

Please refer to correspondence dated, September 27, 2017 which addresses the proposed proprietary name, Jeuveau. 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/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.
 - 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:

Product Quality: Drug Substance



3.

(b) (4)

4. A leachable study is underway for the DS container closure. Leachable substances can induce degradation, precipitation and changes in the product. To allow us to assess the impact of potential leachable substances on the DS, submit the leachable study results for the DS container closure to the BLA. In addition, provide the letters from the DMF holders authorizing you to cross reference Type III DMF (b) (4) and DMF (b) (4).
5. To ensure adequate characterization of a new working cell bank (WCB), qualification of a WCB should include manufacture and characterization of at least one DS lot at commercial scale. Therefore, in addition to the studies you plan to conduct to support qualification of a new WCB, we recommend you plan to manufacture and characterize at least one lot of DS at commercial scale. Update the WCB qualification protocol to include manufacture and characterization of at least one lot of DS and a commitment to place the first DS and DP lot manufactured from the new WCB on stability. Absent an Agency approved WCB qualification protocol at such time as your BLA is approved, you will be required to report qualification of a new WCB in a prior approval supplement.
6. The BLA includes a commitment to place one DS batch on a stability protocol under the (b) (4) storage condition annually (section 3.2.S.7.2). (b) (4)
(b) (4)
(b) (4). Incorporate studies with DS held under appropriate accelerated condition into the annual stability program.
7. You indicated in the “Adventitious Agents Safety Evaluation Report” in Section 3.2.A.2 of the BLA that evaluation of viral clearance (b) (4) (b) (4) are on-going. If these studies are completed at the time of BLA resubmission, provide the results from these studies.

Product Quality: Drug Product

8. We received unsolicited information in an amendment you submitted on December 15, 2017. This information includes process validation data from three new DP lots manufactured with an updated commercial DP manufacturing process. We did not review these data. In addition, we did not review the release and stability data from these new DP lots. If you plan to change the DP manufacturing process and these data support your changes, submit them to us through an appropriate mechanism.
9. The commercial DP shipping validation studies you provided in the BLA include assessment of the temperature of the shipping containers and the physical integrity of the

DP vials during the winter months. This validation study is inadequate and additional information is needed to assess the suitability of your commercial shipping process. Provide the following information:

- a. The validation results do not address the impact of shipping on product quality attributes of the DP. Provide product quality data from the winter shipping studies if they are available.
 - b. During the pre-approval inspection of your facility in November 2017, you indicated that the summer shipping validation had been completed. Update the BLA to include the results from the summer shipping validation and provide product quality data from the summer shipping studies if they are available.
10. In your December 1, 2017 response to the November 13, 2017 information request, you provided 12 months of leachables data for the DP container closure system and indicated that the leachable studies for the container closure system are ongoing. Provide updated leachable study results. If the levels of leachables detected are above the safety limits, provide a risk assessment of their impact to product quality and patient safety and justification for the continued use of the container closure system.

11. In your March 5, 2018 response to the February 21, 2018 information request to clarify what manufacturing steps are

(b) (4)
(b) (4)

12. *Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls*

(b) (4)
(u) (4)

(b) (4). Update this section of the BLA to include the procedures used
(b) (4).

- 13.

(b) (4)

14. The HSA excipient in the DP formulation is supplied by (b) (4). You provided a letter from (b) (4) authorizing you to reference (b) (4), US License No. (b) (4); however, throughout the BLA, you incorrectly refer to Plasma Master File (b) (4). Update your BLA to refer to (b) (4) for which you have a letter of authorization to cross reference.

Microbiology: Drug Substance

15. You committed to implement (b) (4)
(b) (4)
(b) (4). Update the relevant sections of the BLA (b) (4)
(b) (4).

Microbiology: Drug Product

- 16 (b) (4)
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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 Sponsors or Applicants of PDUFA Products,” December 2017 at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547>.

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 Strother D. Dixon, Senior Regulatory Project Manager, at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Julie Beitz, MD
Director
Office of Drug Evaluation III
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/

JULIE G BEITZ
05/15/2018