



Our STN: BL 125563/0

BLA COMPLETE RESPONSE

MCM Vaccine Company
Attention: Ms. Krissy Carrington
Sanofi Pasteur, Inc., Discovery Drive
Swiftwater, PA 18370-0187

November 1, 2015

Dear Ms. Carrington:

This letter is in regard to your biologics license application (BLA) for Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate [Meningococcal Protein Conjugate] and Hepatitis B [Recombinant] Vaccine manufactured at Sanofi Pasteur, Inc. in Toronto, Ontario, Canada, and submitted under section 351 of the Public Health Service Act (42 U.S.C. 262).

We have completed our review of all the submissions you have made relating to this BLA. After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below.

1. The pertactin (PRN) potency assay data indicate that your manufactured lots fail to consistently meet your proposed specification for the (b) (4) vaccine. In the October 1, 2015 amendment to your BLA you provide results for PRN potency from (b) (4) prospective commercial scale (b) (4) lots. The PRN potency data you submitted includes results from both release and stability testing. These data show Out of Specification (OOS) results from PRN potency testing for three lots ((b) (4) at 6 months post-release, (b) (4) at release, and (b) (4) at release). In addition, two lots (b) (4) failed your specification for stage 1 testing at release. We note that your investigation into the root cause for these OOS PRN potency results is ongoing, and you have projected a completion date in the third quarter of 2016.
 - a. Please provide the complete results from your OOS investigation.
 - b. Please provide information and testing data demonstrating that commercial scale lots of (b) (4) can be consistently manufactured with the same PRN testing profiles as those clinical lots used in your pivotal trials and that commercial scale lots would be expected to retain the same PRN potency testing profiles throughout your proposed expiration dating period.
2. In your September 15, 2015, response to Question 5 of our Information Request dated July 27, 2015, you state that lot (b) (4) was manufactured in (b) (4) (b) (4) for measuring “(b) (4) of drug product” as determined by (b) (4).

According to your procedures, this lot can be used as a reference for (b) (4). The approved hold time of lot (b) (4) when used in manufacturing is (b) (4) however, given the initial manufacturing date of (b) (4), lot (b) (4) will be (b) (4) at the end of the (b) (4) period specified for use of this lot as a reference. Please address the following:

- a. Please provide the procedures used to choose and qualify lots as reference standards. Please choose lots that are within their approved manufacturing hold time to be qualified as reference standards.
- b. Your procedures during qualification and during the annual re-evaluation do not include appropriate tests to determine that the quality of the conjugate has been maintained. Please perform additional testing during the qualification and annual re-evaluation to demonstrate that the reference conjugate is within specifications expected for the vaccine. Additional testing could include the normal release panel for PRP-OMPC or orthogonal methods to demonstrate that the conjugate is intact.
- c. Your re-evaluation procedures are based on trending of the (b) (4). Please provide acceptance criteria for the (b) (4) to be used during the re-evaluation.

We reserve final comment on the proposed labeling until the application is otherwise acceptable.

We reserve final comment on the proposed lot release protocol until the application is otherwise acceptable.

We stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response.

Within 10 days after the date of this letter, you should take one of the following actions: (1) amend the application; (2) notify us of your intent to file an amendment; or (3) withdraw the application.

You may request a meeting or teleconference with us to discuss the steps necessary for approval. For PDUFA products please submit your meeting request as described in our “Guidance for Industry: *Formal Meetings Between the FDA and Sponsors or Applicants*,” dated May 2009.

This document is available on the internet at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf> or may be requested from the Office of Communication, Outreach, and

Development, at (240) 402-8020. For details, please also follow the instructions described in CBER’s *SOPP 8101.1: Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants*. This document also is available on the internet at

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm>, or may be requested from the Office of Communication, Outreach, and Development.

Please be advised that, as stated in 21 CFR 601.3(c), if we do not receive your complete response within one year of the date of this letter, we may consider your failure to resubmit to be a request to withdraw the application. Reasonable requests for an extension of time in which to resubmit will be granted. However, failure to resubmit the application within the extended time period may also be considered a request for withdrawal of the application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions regarding the above, please contact the Regulatory Project Managers, Kelsy Hoffman, Ph.D. or Katie Rivers, M.S. at 301-796-2640.

Sincerely yours,

Wellington Sun, M.D.
Director
Division of Vaccines and
Related Products Applications
Office of Vaccine
Research and Review
Center for Biologics
Evaluation and Research