



DATE: September 11, 2018

TO: File: STN # 125563/0.36

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PRODUCT: Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine
Adsorbed, Inactivated Poliovirus, Haemophilus B Conjugate
[Meningococcal Protein Conjugate] and Hepatitis B [Recombinant]
Vaccine, PR5I
(b) (4)

SUBJECT: Response to CBER comment 1, Complete Response Letter

APPLICANT: MCM

1. General Information

Submission Tracking Number (STN): 125563/0
Submission received by CBER: Original submission received 13 August
2014, response to Complete Response letter received 29 June 2018
Review completed: September 11, 2018
Material Reviewed: 125563/0.36, 0.39
Related Master File, INDs and BLAs: STN# 125563/0.21, 14496,
103666/5394 +3, 125145/483 +1, IND 14496

2. Executive Summary

MCM submitted a response to the 1 November 2015 CBER Complete Response Letter. In response to CBER comment 1, MCM provided information supporting the age and weight of the mice used in the Acellular Pertussis Mouse Immunogenicity Assay as the cause for the out of specification (OOS) results observed for the pertactin antigen in (b) (4). In addition, they referenced STN# 125145/483 +1, the prior approval supplement that requested an increase in the age and weight of the mice to be used in the assay when testing Quadracel and Pentacel. The criteria proposed in STN# 125145/483 +1 will be adopted for the release testing of Diphtheria and Tetanus Toxoids

and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, Haemophilus B Conjugate [Meningococcal Protein Conjugate] and Hepatitis B [Recombinant] Vaccine (PR5I).

The response to CBER Comment 1 was adequate. The data provided and cross referenced indicated that the OOS results for the pertactin potency were likely due to the use of immature mice. The implementation of the proposed criteria of (b) (4) for the potency test is appropriate. The data support approval of the product using the proposed criteria for the age and weight of the mice, and the release and stability limits currently applied to the pertussis components of Quadracel.

3. Background

On 13 August 2014, MCM, a company formed by Sanofi Pasteur and Merck, applied for licensure of their combined product: Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, Haemophilus B Conjugate [Meningococcal Protein Conjugate] and Hepatitis B [Recombinant] Vaccine also designated PR5I or (b) (4). A complete response letter (CR) was issued on 1 November 2015 due to deficiencies in product testing. One of the deficiencies was the rate of out of specification (OOS) results for the potency of the pertussis component pertactin (PRN) (Comment 1, CR letter, see also memo from Juan Arciniega, dated 21 October 2015). This memo reviews the applicant's responses to Comment 1, submitted 31 July 2018.

In August 2016, Sanofi submitted a prior approval supplement under STNs 103666/5394 (primary), BL 125111/613, BL 125145/386, BL 125525/30 to update the age and weight criteria for mice used in the Acellular Pertussis Mouse Immunogenicity Assay. The applicant had performed investigations into OOS results across all pertussis containing products and concluded that changes to the (b) (4) at the vendor and ordering practices had resulted in the use of immature mice in the pertussis potency testing. The use of immature mice led to the higher than expected rate of OOS results for PRN potency. Under those prior approval supplements, the sponsor requested a change in the age and weight criteria for the mice to (b) (4). Those applications were approved 17 November 2016 and the criteria also applied to the testing of PR5I.

On 25 May 2017, Sanofi submitted a meeting package to IND 14496, amendment 104, that included their investigation into the PRN potency OOS results for PR5I. The applicant's conclusions were that the use of immature mice in the potency test and the use of (b) (4) were the causes of the OOS results. Consistent with the criteria approved under STNs 103666/5394 +3, they proposed age and weight criteria for the mice of (b) (4). CBER concurred (see correspondence under IND 14496 dated 1 August 2017).

On 24 May 2018, Sanofi submitted a prior approval supplement under STNs 125145/483 and 125525/100 requesting an additional modification of the criteria for the

age and weight of the mice used in the pertussis potency testing. In the response to the CR letter issued for 125563/0, the applicant references these submissions and indicates that the new age and weight criteria will also apply to PR5I. The data in that supplement were found to support the proposed increase in the age and weight criteria to (b) (4) when testing Quadracel and Pentacel. The supplement was approved 6 September 2018. See my memo to STN 125145/483 dated 28 August 2018.

4. Review

CBER comment 1 is listed below in bold. A summary of the response and review follows in plain text.

The Pertactin (PRN) potency assay data indicate that your manufactured lots fail to consistently meet your proposed specification for (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 PRN potency testing profiles throughout your proposed expiration dating period.

The applicant provided a summary of the OOS investigation, the results of potency testing of PR5I using standardized mouse criteria, a statistical analysis of the mouse immunogenicity data collected from results of PR5I (b) (4) filled product potency testing from 2016 to present, and proposed additional steps to improve performance of the Acellular Pertussis Mouse Immunogenicity Assay (potency test).

Results from two studies were provided: Report Q_0565320 v.2.0, "Investigation of the Impact of Female (b) (4) Mouse Weight on PRN Mouse Immunogenicity Results," and Report Q_0584397 v.1.0, "Examine Impact of Mouse Age at Time of Immunization on PRN Responses using Female (b) (4) Mice (b) (4) of Age at Immunization."

Report Q_0565320 v.2.0 described (b) (4)



Report Q_0584397 v.1.0 described (b) (4)



Overall the data support an effect of mouse age and weight on the performance of the pertussis potency test for PRN. See also my memo to STN 125145/483 for additional data that support the effects of the mice age and weight on the performance of the potency test.

The applicant provided an updated summary table (Table 3) of the PRN potency data from all lots tested for either the European market or US licensure from December 2015 to present. Of the (b) (4) lots with data at the time of release, only two were reported as OOS. One OOS lot was tested in early 2016 and the other in late 2017/early 2018. Three lots had failed to meet the criteria for first stage testing but met the criteria at the second stage. One lot failed to meet the first stage criteria but data from the second stage are pending. The table also included data from stability testing. Two lots tested in 2016 were OOS, one at the 6-month time point, the other at the 36-month time point. No other results of a total of (b) (4) tests were OOS. The data are insufficient to evaluate the effect the change in mouse weight criteria may have on future testing.

The applicant proposed to change the limits for acceptable potency for all four pertussis antigens from the limits applied to the DTaP-IPV vaccine (Quadracel) to product specific limits. The proposed limits were based on the four clinical lots, stability lots to support the (b) (4) presentation, and U.S. and commercial lots. Lots that were OOS based on the current acceptance criteria were excluded from the analysis. The applicant also noted that the criteria for PR5I as licensed by the EU was product specific. Table 4 indicated that a total of (b) (4) tests were used to establish the proposed limits. However, the proposal raised several concerns. The tests included those for stability; the use of stability data to set release specifications is not generally accepted. In addition, the number of lots included in the analysis used versus the data from repeat testing was not provided. The data on which the new limits were based may be biased and not reflect the variability of the test or manufacturing. The limits for the potency of the pertussis components of PR5I should remain consistent with those for DTaP-IPV.

The applicant's discussion of additional steps to improve the performance of the acellular pertussis mouse immunogenicity assay was limited to the intention to apply the mouse weight and age criteria proposed in STN #124145/483 to the testing for PR5I. The implementation of the criteria for testing of PR5I is appropriate.

The following information request was sent to the applicant on 17 August 2018.

Regarding your Response to the Complete Response Letter (CRL) dated 02 November 2015 for BL 125563, we have the following information request:

We have reviewed your response to CBER comment 1 and do not agree that sufficient product release data are available, generated using the proposed pertussis potency test with the revised mouse age and weight criteria, to support the change to the potency limits proposed for this product. Please revise the potency limits to coincide with the limits set for Quadracel®. Values must be (b) (4) :

(b) (4)

The sponsor agreed and submitted appropriately updated Modules 3.2.P.2 and 3.2.P.5.

5. Recommendation

The data support the approval of the product with the implementation of the (b) (4) age and weight criteria for the mice used in the Acellular Pertussis Immunogenicity Assay of (b) (4) . The release criteria for the potency of the pertussis components will coincide with the limits set for Quadracel.