



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH**

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**MEMORANDUM**

**Date:** October 21, 2015  
**From:** Juan L. Arciniega, LRSP/DBPAP  
**To:** File for STN 125563/0  
**Through:** Michael Schmitt, Chief, LRSP/DBPAP  
**Subject:** Pertussis Component Assay Review  
**Product:** Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP), Inactivated Poliovirus (IPV), Haemophilus b Conjugate (Hib) and Recombinant Hepatitis B Vaccine (HepB)(b) (4) .  
**Applicant:** MCM Vaccine Company, Swiftwater, PA

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**1 EXECUTIVE SUMMARY**

The purpose of this Biologics License Application (BLA) from MCM Vaccine Company (MCM) is to license Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP), Inactivated Poliovirus (IPV), Haemophilus b Conjugate (Hib) and Recombinant Hepatitis B Vaccine (HepB) vaccine (PR5I), trade name (b) (4) indicated for the active immunization against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B and invasive disease due to *Haemophilus influenzae* type b, as a three dose series in children from 6 weeks through 4 years

of age. The pertussis component of PR5I and of four other U.S.-licensed combination vaccines manufactured by Sanofi Pasteur Limited (SPL) contains the same purified antigens used to formulate (b) (4). In addition, the drug products that constitute PR5I are formulated in U.S.-licensed facilities, and the manufacturing process (including testing and release criteria for the pertussis drug substances) and pertussis testing and release criteria proposed for PR5I final drug product are identical to those for the pertussis component of Pentacel<sup>®</sup>, U.S.-licensed DTaP-IPV/Hib combination vaccine, with the exception of the (b) (4). The rationale for using the same acceptance criteria for the final drug product bulks of both vaccines is that the concentration of the pertussis antigens per dose is identical in both cases. Since Pentacel<sup>®</sup> licensing in 2008, CBER has released approximately 110 lots of this vaccine using these or analogous tests and criteria. Results of Pentacel<sup>®</sup> pertussis testing at release and as part of its formal stability testing program, support the suitability of the tests and specifications for the DTaP-IPV component of Pentacel<sup>®</sup> and Quadracel<sup>®</sup> (DTaP-IPV, licensed on March 24, 2015) and therefore for (b) (4). Concerning the (b) (4) test, MCM originally proposed a specification of (b) (4) deaths for release and for stability testing. However, after careful consideration of all the information submitted in the original application and subsequent amendments, CBER decided that the specifications will be (b) (4) deaths at release and (b) (4) at all stability time points. On the other hand, the PRN mouse immunogenicity assay has recently failed in several instances to meet the proposed specification for (b) (4). MCM has not shown that the problem that led to these outcomes has been resolved. Therefore, pending the opinion of other reviewers, I recommend that a Complete Response (CR) Letter be issued for this BLA.

## 2 REVIEW

### 2.1 Background

MCM submitted this Biologics License Application (BLA) for PR5I on August 13, 2014, for which the trademark (b) (4) has been proposed. All PR5I pertussis antigens are components of combination vaccines currently licensed in the US by SPL of Toronto, Canada, including the DTaP component contained in STN 125145 Pentacel<sup>®</sup> and STN 125525 Quadracel<sup>®</sup>. The 5-component acellular pertussis adsorbed portion of PR5I includes per dose 20 µg of Pertussis Toxoid (PT), 20 µg of Filamentous Haemagglutinin (FHA), 3 µg of Pertactin (PRN), and 5 µg of Fimbriae Types 2 and 3 (FIM), same formulation than Pentacel<sup>®</sup> and Quadracel<sup>®</sup>. Because the pertussis antigens used to formulate (b) (4) are manufactured in identical way than those used to formulate Pentacel<sup>®</sup> and four other pertussis-containing US-licensed combination vaccines, the proposed testing, system suitability criteria for the assays and specifications for the pertussis antigens in (b) (4) are very similar or identical to those in Pentacel<sup>®</sup>, with the notable exception of the proposed specification for the (b) (4) in final drug product.

**2.2 Review**

(b) (4) [Redacted]

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(b) (4)



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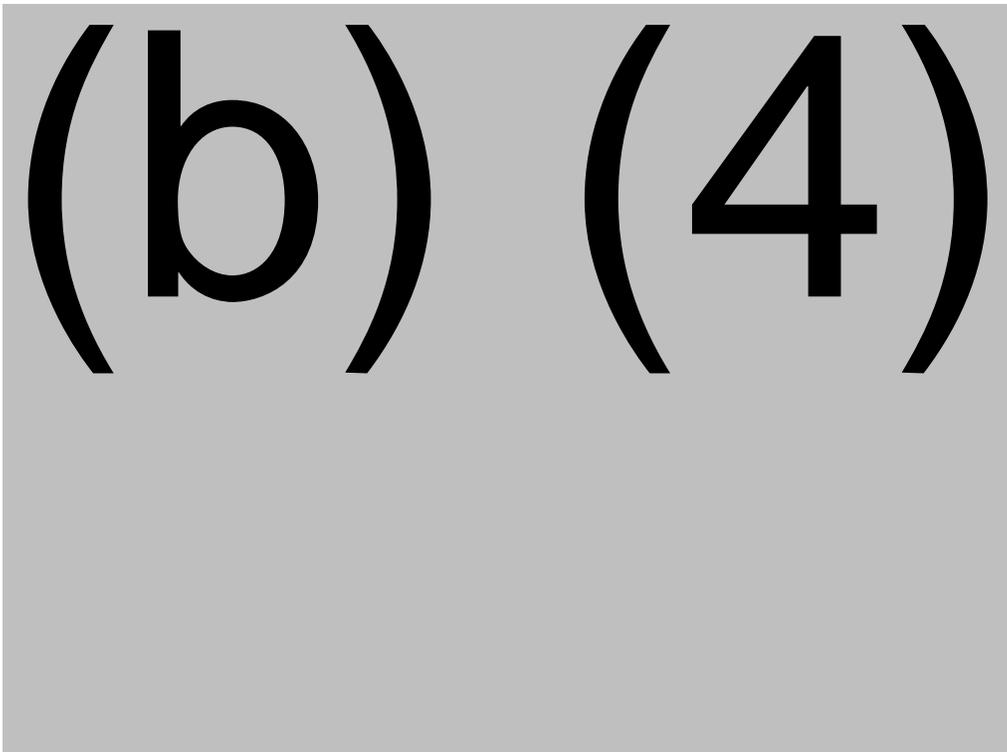
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**2.2.4 PR5I Final Bulk Drug Product pertussis specifications**

(b) (4)



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30 Pages Determined to be Not-Releasable: (b)(4)

(b) (4)

[Redacted]

A meeting was convened on October 7, 2015, to discuss amendment 22. At the meeting, the Office of Vaccines Research and Review management heard and agreed with the basis for the issuance of a CR Letter for this STN, considering the recent PRN immunogenicity results on PR5I and the lack of an appropriate root cause study of those results.

### 3 DISCUSSION

MCM originally proposed a new specification for the (b) (4) test of PR5I (b) (4).

(b) (4)

(b) (4)



In contrast, no decision regarding the suitability of the testing and specifications of the mouse immunogenicity assay for PR5I can be made at this time. In particular, the PRN mouse immunogenicity assay has recently failed in several instances to meet the proposed specification for PR5I. MCM has not shown that the problem that led to these outcomes has been resolved, and it is in the process of adequately identifying a root cause, before proceeding to propose a corrective action.

#### 4 RECOMMENDATION

Based on my review of the data, I recommend that a Complete Response Letter be issued for this BLA.

At the meeting referenced above (October 7, 2015), the following language was proposed for the CR letter:

*The Pertactin (PRN) mouse immunogenicity assay fails to consistently meet the proposed specification for the (b) (4) vaccine. In Section 1.11.1 of BLA amendment STN 125563/0.22 submitted on October 1, 2015, Table 4 shows PRN Immunogenicity results for (b) (4) prospective commercial scale (b) (4) lots that were tested at release and as part of the proposed stability program. PRN immunogenicity testing revealed that three of these lots gave Out of Specification (OOS) results, while two additional lots failed to meet specification for stage 1 testing. We acknowledge that the investigation into the root cause for these OOS results is ongoing with a projected completion date of Quarter 3 2016. To demonstrate that the PRN potency test is performing in an acceptable manner, the results of the investigation should be provided as well as information and testing data demonstrating that commercial scale lots of (b) (4) can consistently be manufactured such that they have the same PRN testing profiles as lots that were shown to be effective in the clinic and that these lots would be expected to retain that profile throughout their dating period.*