



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

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**From:** Tod J. Merkel, LRSP/DBPAP  
**To:** File  
**Through:** Michael Schmitt, Chief, LRSP/DBPAP  
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**Title:** 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) ) CMC Review Pertussis Component.  
**Applicant:** MCM Vaccine Company

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## 2. Executive Summary:

PR5I is a hexavalent combination vaccine being co-developed by Sanofi Pasteur and Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. [Merck]. A new company, MCM Vaccine Co., was created to manufacture and license this vaccine. PR5I is manufactured using modified and/or existing bulk intermediates from vaccines licensed in the US by Sanofi Pasteur and Merck. The target indication for PR5I is for active immunization against diphtheria, tetanus, pertussis, poliomyelitis (caused by poliovirus Types 1, 2, and 3), invasive disease caused by Haemophilus influenzae type b and infection caused by all known subtypes of Hepatitis B virus. PR5I is a sterile fully liquid preservative-free suspension presented as a single dose in a vial for intramuscular injection in infants at 2, 4, and 6 months of age.

The seed culture, fermentation, purification, detoxification and storage of the pertussis adsorbed antigens used in the PR5I vaccine are the same as that for Pentacel<sup>®</sup>, with the exception that (b) (4). Therefore, there are no concerns about the manufacture of the adsorbed bulk pertussis antigens used to formulate PR5I. However, due to the (b) (4), a demonstration of stability of the pertussis antigens in the adsorbed antigen bulks, bulk drug product and final drug product is required. In addition, in Pentacel<sup>®</sup> (DTaP-IPV-ActHIB), the pertussis antigens, diphtheria toxoid, tetanus toxoid and inactivated polio virus component are combined in a liquid suspension (DTaP-IPV component) that is combined with a lyophilized ActHIB vaccine component immediately before administration. In PR5I, all six components are formulated into a single liquid, preservative free suspension. Due to the changed formulation relative to Pentacel<sup>®</sup>, a demonstration of stability of the pertussis antigens in the bulk drug product and final drug product is required. The stability of the pertussis antigens in the adsorbed antigen bulks, bulk drug product and final drug product was reviewed and found to be acceptable with one exception. (b) (4)

The company has committed to conduct these studies post-licensure and has proposed an acceptable plan for collecting the required data.

With respect to the pertussis component, the only CMC concern is the issue of (b) (4) in the final formulated product. It is not yet clear if PR5I has (b) (4), I recommend approval of this biological license application.

### 3. Pertussis Component CMC Review:

#### 3.1 Background:

A partnership was established between Sanofi Pasteur Inc. and Merck Sharp and Dohme Corp (hereafter designated “Merck”) to support the co-development and commercial manufacturing of a Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate [Meningococcal Protein Conjugate] and Hepatitis B [Recombinant] (PR5I) Vaccine. PR5I is a hexavalent vaccine being developed to provide protection against these six childhood diseases with a single injection.

Each 0.5 mL dose contains:

- 15 Lf Diphtheria Toxoid Adsorbed
- 5 Lf Tetanus Toxoid Adsorbed
- 20 µg Pertussis Toxoid (PT)
- 20 µg Filamentous Hemagglutinin (FHA)
- 3 µg Pertactin (PRN)
- 5 µg Fimbriae Types 2 and 3 (FIM)]
- 29 D antigen units (DU) Type 1 (Mahoney) Poliomyelitis virus
- 7 DU Type 2 (MEF-1) Poliomyelitis virus
- 26 DU Type 3 (Saukett)] Poliomyelitis virus
- 3 µg PRP- polyribosylribitol phosphate of Haemophilus influenza type b covalently bound to 50 µg of OMPC-outer membrane protein complex of Neisseria meningitides serogroup B
- 10 µg Hepatitis B surface antigen (HBsAg).

This review is limited to review of the pertussis component. The five acellular pertussis adsorbed antigens [Pertussis Toxoid (PT), Filamentous Haemagglutinin (FHA), Pertactin (PRN) and Fimbriae Types 2 and 3 (FIM)] are derived from *Bordetella pertussis* cultures. PT is detoxified by treatment with glutaraldehyde and FHA is treated with formaldehyde to detoxify residual PT. PRN and FIM do not require detoxification. The individual antigens are adsorbed separately onto aluminum phosphate. (b) (4) for the acellular pertussis adsorbed drug substance of PR5I Vaccine is the same as that for the U.S. licensed vaccine Pentacel<sup>®</sup>. Fermentation, purification, detoxification and storage of the pertussis adsorbed antigens used in the PR5I vaccine is the same as that for Pentacel<sup>®</sup>, with the exception that (b) (4). Therefore there are no concerns over the manufacture of the adsorbed bulk pertussis antigens used to formulate PR5I. The release and stability testing of the adsorbed bulks in the (b) (4), the release and stability testing of the bulk drug substance and the release and stability testing of the drug product are reviewed below.

The Pentacel<sup>®</sup> eBLA contains CMC documentation for the manufacture of the acellular pertussis antigens up to the pre-adsorbed concentrate stage in both Building (b) (4) and Building (b) (4), however, for these components of PR5I vaccine only adsorbed antigen produced in Building (b) (4) will be used therefore only Building (b) (4) will be licensed for the production of PR5I.

**3.2 Drug Substance:**

(b) (4)



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

(b) (4)

### 3.3.2 Release Testing of Final Drug Product:

**Table 2: Release and Shelf-life Specifications for PR5I Filled Product (Unlabeled)**

Test	Method Reference	Release Acceptance Criteria	Shelf-life Acceptance Criteria
Physical Appearance	In-house	Uniform, cloudy, white to off-white suspension	Same as Release
Sterility	(b) (4)	No microbial growth	Same as Release

Test	Method Reference	Release Acceptance Criteria	Shelf-life Acceptance Criteria
(b) (4)	(b) (4)	(b) (4)	Same as Release
Aluminum Content	(b) (4)	(b) (4)	NA
Extractable Volume	(b) (4)	≥ 0.5 mL	NA
Pyrogen	(b) (4)	Non-Pyrogenic	NA
General Safety Test - Modified	In-house (Modified CFR 610.11)	(b) (4)	NA

Note: Exemption for General Safety Test is requested in the BLA, however the commercial launch lots will be tested until exemption granted by CBER upon approval of PR5I License, see [3.2.P.5.6 Justification of Specifications](#).

**Table 3: Release Specification for PR5I Labeled Filled Product**

Test	Method Reference	Acceptance Criteria
Identity (b) (4)	In-house	HBsAg and OMPC components detected
<b>Alternate Identity Test</b>		
Identity (b) (4)	In-house	PRP-OMPC Detected
Identity (b) (4)	In-house	HBsAg Detected

**3.3.3 Release Testing of Final Bulk Product:**

- (b) (4)
- [Redacted content]

### 3.3.4 Release Testing of Finished Product:

All release criteria were met for the (b) (4) finished product lots tested (Section 3.2.P.8.3).

### 3.3.5 Stability of Drug Product

PR5I Final Bulk Product is stored at (b) (4). The shelf-life of PR5I Vaccine proposed in the original submission was 36 months from the date of Final Bulk Product formulation. In a subsequent amendment, the applicant extended the proposed shelf-life of PR5I Vaccine to 42 months. Stability data for the Final Bulk Product and Finished Filled Product was provided in Section 3.2.P.8.3.

The tests performed to demonstrate stability of the drug product include: (b) (4) physical appearance, specific toxicity, D-antigen content, sterility, Diphtheria potency (b) (4) (b) (4)), Tetanus potency (b) (4) (b) (4)), Pertussis immunogenicity ((b) (4) (b) (4)), Pertussis immunogenicity (Mouse), (b) (4) (b) (4) IPV immunogenicity, (b) (4) (b) (4), HBsAg IVRP, (b) (4) (b) (4), PRP content, and (b) (4) (b) (4).

The initiation date for the PR5I stability studies (i.e. time (b) (4)) is the date of formulation of the PR5I (b) (4) Product

### 3.3.6 Final Bulk Product Stability

(b) (4) [Redacted]

### 3.3.7 Final Drug Product Stability:

Time zero (0) for the Finished (Filled) Product stability studies is the date of formulation of the (b) (4) [Redacted] lots met all release and stability specifications with the following exceptions:

- PR5I Finished Product Lot (b) (4) failed (b) (4) [Redacted] at time = 0 and at 36 months Passed Pertussis Mouse Immunogenicity out to 48 months.

- PR5I Finished Product Lot (b) (4) failed the (b) (4) assay at 42 months.
- PR5I Finished Product Lot (b) (4) failed (b) (4) at time = 0

Note: The (b) (4) assay is performed for release outside the U.S. The (b) (4) assay is used for release in the U.S.

**Stability Commitments:**

The applicant commits to continue the on-going stability studies that have been initiated (Protocol number B014063) on the (b) (4) consistency PR5I Vaccine lots (b) (4) (Protocol number B015684) on the one PR5I Vaccine lot (b) (4). The studies will be performed on the product at storage conditions of 2°C to 8°C for up to and including 48 months. Any out of specification results will be reported to CBER.

Each year that PR5I Vaccine is filled, (b) (4) PR5I Vaccine for marketed presentation will be monitored for stability. The samples for this stability program will be tested at time points 0, 12, 24 and 36 months while stored at 2°C to 8°C.

(b) (4)

**Stability Conclusions:**

(b) (4)

Stability of PR5I Final Bulk Product lots (b) (4)

Taken together, the results of stability testing support storage of the Final Bulk Product for the proposed hold time of (b) (4) before filling and support the originally proposed shelf life of 36 months for the Final Filled Drug Product.

Although the release testing and stability testing results presented in this submission support the proposed shelf life of the pertussis adsorbed bulk antigens and the final bulk product and the

originally proposed shelf life for the final filled drug product (36 months), the data raise concerns about (b) (4) in PR5I. This issue is being addressed in detail by other members of the product review team.

#### **Component Information Table**

I reviewed the components that are used to manufacture the pertussis antigens in the PR5I vaccine and no discrepancies were identified. The raw materials and all other ingredients including all components of animal origin are (b) (4) to the components used in the manufacture of the Pentacel vaccine, and are, therefore, free of adventitious agents and acceptable for use in the production of PR5I.

#### **4. Recommendation.**

With respect to the pertussis component, the only CMC concern is the issue of (b) (4) in the final formulated product. (b) (4) approval of the other review disciplines, I recommend approval of this biological license application