



**CBER REGULATORY REVIEW MEMORANDUM**

**Date** 24 June, 2015

**From** Dr. Hyesuk Kong  
Laboratory of Microbiology, *In-Vivo* Testing and Standards (LMIVTS)  
Division of Biological Standards and Quality Control (DBSQC)  
Office of Compliance and Biologics Quality (OCBQ)  
Center for Biologics Evaluation and Research (CBER)  
Food and Drug Administration (FDA)

**To** Biologics License Application Submission Tracking Number # 125563/0

**Subject** BLA: Review of Bioburden, Bacterial Endotoxin, Sterility, Specific Toxicity, Diphtheria/Tetanus *in-vivo* Potency, and Pyrogen Method Qualifications for Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate [Meningococcal Protein Conjugate] and Hepatitis B [Recombinant] Vaccine (DTaP-IPV-Hib-HepB / PR5I), (b) (4)

**Through** Dr. James Kenney, Chief, LMIVTS/DBSQC/OCBQ/CBER/FDA  
Dr. William M. McCormick, Director, DBSQC/OCBQ/CBER/FDA

**Applicant** MCM Vaccine Company (Co-developed by Sanofi Pasteur and Merck)

**Product** Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate [Meningococcal Protein conjugate] and Hepatitis B [Recombinant] Vaccine (DTaP-IPV-Hib-HepB / PR5I), (b) (4)

**Biologics License Application (BLA) Submission Tracking Number (STN)** 125563/0

**Submission Received by CBER** 13 August, 2014

**Review Completed** 24 June, 2015

**Material Reviewed**

Method qualifications for: 1) burden performed for in process control at stage of the (b) (4); 2) (b) (4) bacterial endotoxin test (b) (4)-BET on (b) (4) production step; 3) Sterility, Specific Toxicity, Diphtheria and Tetanus Potency performed on the (b) (4); 4) Pyrogen Test on the final container (FC) product; and MCM's response to CBER's

Information Requests (IRs: amendments 125563/0/6 and 125563/0/10; received on 9 April and 28 May of 2015, respectively).

### Executive Summary

After a thorough review of this BLA and the response to CBER's IRs, this reviewer finds Sanofi's bioburden, <sup>(b) (4)</sup>-BET, and sterility test methods were qualified in accordance with (b) (4) [REDACTED], respectively, by demonstrating the tested matrixes are suitable for these intended test methods. In addition, this reviewer finds the rabbit pyrogen test was performed and is compliant with (b) (4) [REDACTED] and the tests for specific toxicity and Diphtheria and Tetanus potency are performed in accordance with (b) (4) [REDACTED] and regulatory Minimum Requirements of the United States Department of Health, Education and Welfare Public Health Service, National Institutes of Health (NIH). Therefore, based on the scope of this review, I recommend approval this BLA.

### Background

MCM Vaccine Company (MCM), formed by Sanofi Pasteur SA (Sanofi) and Merck, Sharp and Dohme, Corp (Merck), submitted this BLA on 14 August, 2014 for the licensed approval of a combined Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate [Meningococcal Protein Conjugate] and Hepatitis B [Recombinant] Vaccine (DTaP-IPV-Hib-HepB), referred to as PR5I. The proposed trade name of this product is (b) (4) [REDACTED].

PR5I is a hexavalent combination vaccine and supplied as a sterile fully liquid preservative-free, cloudy, white to off-white suspension presented as a single dose in a vial for intramuscular injection. PR5I is indicated for active immunization against diphtheria, tetanus, pertussis, poliomyelitis (caused by poliovirus Types 1, 2, and 3), against invasive disease caused by *Haemophilus influenzae* type b (Hib) and infection caused by all known subtypes of hepatitis B virus in infants at 2, 4, and 6 months of age.

PR5I is manufactured using modified and /or existing bulk intermediates from vaccines already licensed in the United States by Sanofi and Merck. Antigenic composition of PR5I per 0.5 mL dose contains: 15 Lf Diphtheria Toxoid Adsorbed, 5 Lf Tetanus Toxoid Adsorbed, 5-Component Acellular Pertussis Adsorbed Antigens (20 µg Pertussis Toxoid [PT], 20 µg Filamentous Hemagglutinin [FHA], 3µg Pertactin [PRN], 5 µg Fimbriae Types 2 and 3 [FIM]), Inactivated Vero Trivalent Poliomyelitis Vaccine (vIPV: 29D Antigen units [DU] Type 1 [Mahoney], 7 DU Type2 [MEF-1], 26DU Type 3[Saukett]), 3 µg polyribosylribitol phosphate (PRP) of *Haemophilus influenzae* type b covalently bound to 50µg of outer membrane protein complex (OMPC) of *Neisseria meningitidis* serogroup B, and 10 µg Hepatitis B surface antigen (HBsAg).

PR5I Final Bulk (FB) manufacturing process consists of (b) (4) [REDACTED]

[REDACTED] before it is filled, labeled and packaged.

The Division of Biological Standards and Quality Control (DBSQC) reviews BLAs and their supplements to ensure analytical methods are appropriate, properly validated and the product matrix is suitable for the intended test method. DBSQC also reviews release specifications for microbial and endotoxin testing to ensure they reflect process capability and meet regulatory compliance. These review activities support DBSQC's lot-release mission, which is the confirmatory testing of submitted product samples and review of manufacturers' lot-release protocols to ensure biological products are

released according to licensed test methods and product specifications. Therefore, this review will focus on: 1) the bioburden method performed on the (b) (4) step, 2) (b) (4)-BET method qualification on the (b) (4), 3) sterility, specific toxicity, Diphtheria/Tetanus *in-vivo* potency, and pyrogen method qualifications on their (b) (4) FC of PR5I to ensure regulatory compliance.

**Review**

Bioburden Test Qualification for (b) (4)

The in-process bioburden test method qualification was performed on (b) (4)

[Redacted]

[Redacted]

(b) (4) BET (b) (4)-BET) Method Qualification

Sanofi qualified their (b) (4)-BET for the (b) (4) by testing (b) (4)

[Redacted] The qualification results were submitted in their analytical method validation report Q\_0256526.

(b) (4)  
[Redacted]

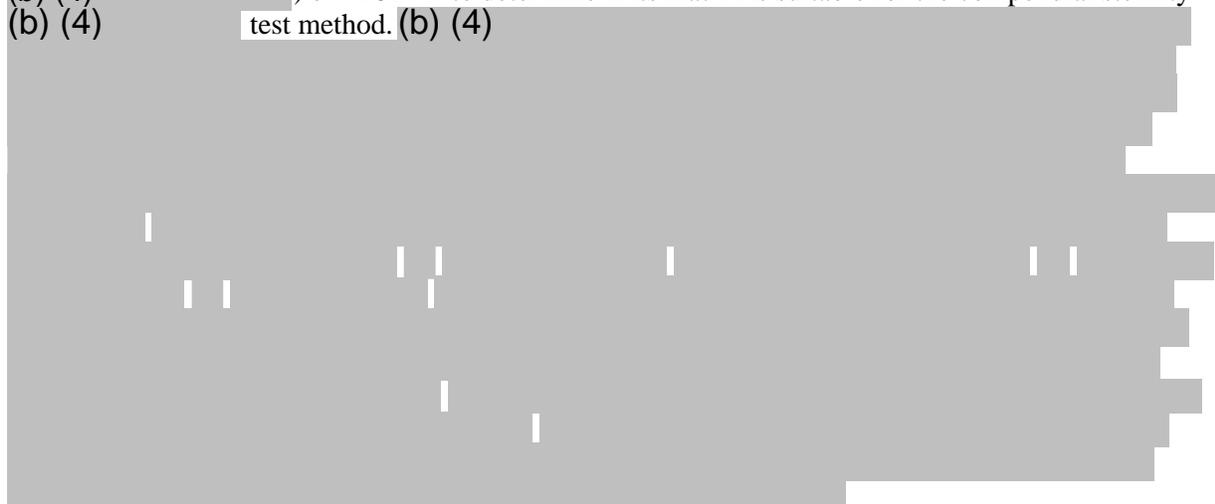
(b) (4)



After review of the test qualification results, this reviewer concludes their (b) (4) -BET was performed and qualified in accordance with (b) (4)

Sterility Test Qualification for PR5I FB

(b) (4) qualification studies were performed on (b) (4) lots (i.e., lot number: (b) (4) ) of PR5I FB to determine if its matrix is suitable for the compendial sterility (b) (4) test method. (b) (4)

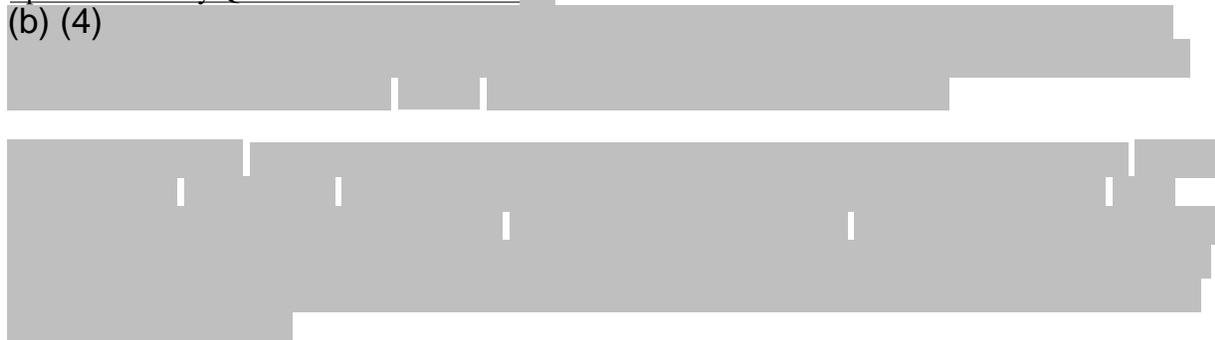


(b) (4)



Specific Toxicity Qualification of the PR5I (b) (4)

(b) (4)



(b) (4)

Diphtheria and Tetanus Potency Testing of the PR5I FB

The Diphtheria and Tetanus *in-vivo* potency test was used to determine that the potency of the Diphtheria and Tetanus Toxoid components in the PR5I vaccine meet the following regulatory NIH Minimum Requirements:

1. The Minimum Requirements for Diphtheria Toxoid (4<sup>th</sup> revision – March 1, 1947);
2. The Minimum Requirements for Tetanus Toxoid (4<sup>th</sup> revision – December 15, 1952); and
3. The Minimum Requirements (Tetanus and Diphtheria Toxoids Combined Precipitated Adsorbed [for adult use], August 25, 1953 – Amendment #1).

Immunization phase: The *in-vivo* potency test method requires (b) (4)

Tetanus Potency

Sanofi performed the Tetanus potency test with vaccine lots used in the phase III clinical trial and post phase III lots (i.e., (b) (4) ) to determine if the antitoxin potency of serum obtained from GPs immunized with PR5I Vaccine meets specification.

(b) (4)

Diphtheria Potency

The Diphtheria potency test method qualification was performed using vaccine lots from their phase III clinical trial and post phase III lots (i.e., (b) (4) ) to determine the antitoxin potency of serum obtained from GPs immunized with PR5I vaccine meets specification.

(b) (4)

(b) (4)



#### Rabbit Pyrogen Test

A rabbit pyrogen test method qualification was performed on (b) (4) clinical lots (i.e., Phase IIa [lots: (b) (4)], Phase IIB [lot: (b) (4)] and Phase III [lots: (b) (4)]) of their PR5I FC product at release and during stability (i.e., 0, 12, 24, 30, 36, 42 months) to determine if the product induces a pyrogenic response in rabbits. The pyrogen dose was determined based on the dose established for (b) (4)



The test was performed and compliant with (b) (4)

#### **Conclusions**

After a thorough review of the information submitted in this BLA and the response to CBER's IRs (amendments 125563/0/6 and 125563/0/10); this reviewer finds MCM's bioburden, (b) (4)-BET, and sterility, test methods were qualified in accordance with (b) (4) respectively, by demonstrating the PR5I matrix is suitable for these intended test methods. In addition, this reviewer finds the rabbit pyrogen test was performed and is compliant with (b) (4) and the tests for specific toxicity and Diphtheria and Tetanus potency were performed in accordance with (b) (4) NIH Minimum Requirements. Therefore, based on the scope of this review, I recommend approval this BLA.