DEPARTMENT OF HEALTH & HUMAN SERVICES
FDA/CBER/OVRR/DBPAP

Food & Drug
Administration
1401 Rockville Pike
Rockville, MD 20852

MEMORANDUM

Date: 06 February 2015

From: James E. Keller, Ph.D.
Tetanus and Diphtheria Toxoid CMC Reviewer
Division of Bacterial, Parasitic and Allergenic Products
Office of Vaccine Research and Review
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration (FDA)

To: Biologics License Application Submission Tracking Number # 125525/0
Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliovirus (DTaP-IPV) Vaccine
5th dose booster in US children 4 to 6 years of age

Subject: Product Review Memo, Tetanus Toxoid and Diphtheria Toxoid Manufacturing and Testing

Through: Michael Schmitt, Chief
OVRR/DBPAP/LRSP

Applicant: Sanofi Pasteur Limited, Toronto

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General Information
STN 125525/0 Original BLA, Sections 3.2.S, Section 3.2 P and Section 3.2 R
STN 125525/0.1 (amendment, 4/14/2014)

Executive Summary
Sanofi Pasteur is seeking licensure of their Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliovirus (DTaP-IPV) Vaccine as a 5th dose booster in children 4 to 6 years of age. The BLA includes a request for Proprietary Name Review for the name Quadracel. Tetanus Toxoid Adsorbed and Diphtheria Toxoid Adsorbed drug substances in Quadracel are the same components made by this manufacturer for use in Pentacel (STN 125145). The firm has cross-referenced the CMC sections of Quadracel with Pentacel's file. No additional CMC data was submitted.

Pentacel contains antigens against five diseases: diphtheria toxoid, tetanus toxoid, acellular pertussis antigens, inactivated polio virus and hemophilus polysaccharide conjugate (Hib). Pentacel was licensed as a combination of three previously licensed vaccines, Daptacel™ (STN 103666), IPOL™ (STN 103930) and ActHIB™ (STN 103935). Daptacel-IPOL is a liquid suspension of diphtheria, tetanus, acellular pertussis and inactivated polio virus, adsorbed. The Hib component in Pentacel™ is ActHib™, which is a lyophilized vaccine in a separate, second vial. The two-vial presentation of Pentacel is approved for bed-side combination where the liquid components of Daptacel-IPOL is added to lyophilized ActHIB™, then immediately injected. Pentacel™ is licensed as a four-dose regimen to be given between the ages of 6 weeks through 4 years of age. In the current BLA, Quadracel is proposed to be used as a fifth booster dose to be given upon completion of the Pentacel™ regimen between the ages of 4 and 6 years. Quadracel is a 0.5 mL, single dose presentation supplied in a single 3-mL glass container. The vaccine is to be administered by intramuscular injection.

Quadracel is manufactured and tested at the same location, made according to the existing license for Pentacel™ with the exception of the ActHib™ vial, which is excluded from the packaging. The manufacturing process for each toxoid component, including in-process testing (b) (4) are identical between Quadracel and Pentacel™. Similarly, the final Quadracel formulation is made using the identical filling process as Daptacel-IPOL. This includes the order of antigen formulation, quantity of each antigen, release testing, release specifications, and stability testing programs for (b) (4) final product. Because Tetanus Toxoid Adsorbed and Diphtheria Toxoid Adsorbed are identical to these toxoid components used to manufacture Pentacel™, the review of tetanus and diphtheria toxoid manufacture was conducted previously during the BLA review of Pentacel™. A summary of the manufacturing process for each toxoid is presented below.

Review
Section 3.2.S.2.1, Manufacturing Sites

Manufacturing sites for tetanus toxoid adsorbed and diphtheria toxoid adsorbed are provided below.

Manufacturing sites	Responsibilities
Sanofi Pasteur Limited 1775 Steeles Ave, West Toronto, Ontario, Canada	Manufacture of Diphtheria Toxoid Adsorbed and Tetanus Toxoid Adsorbed

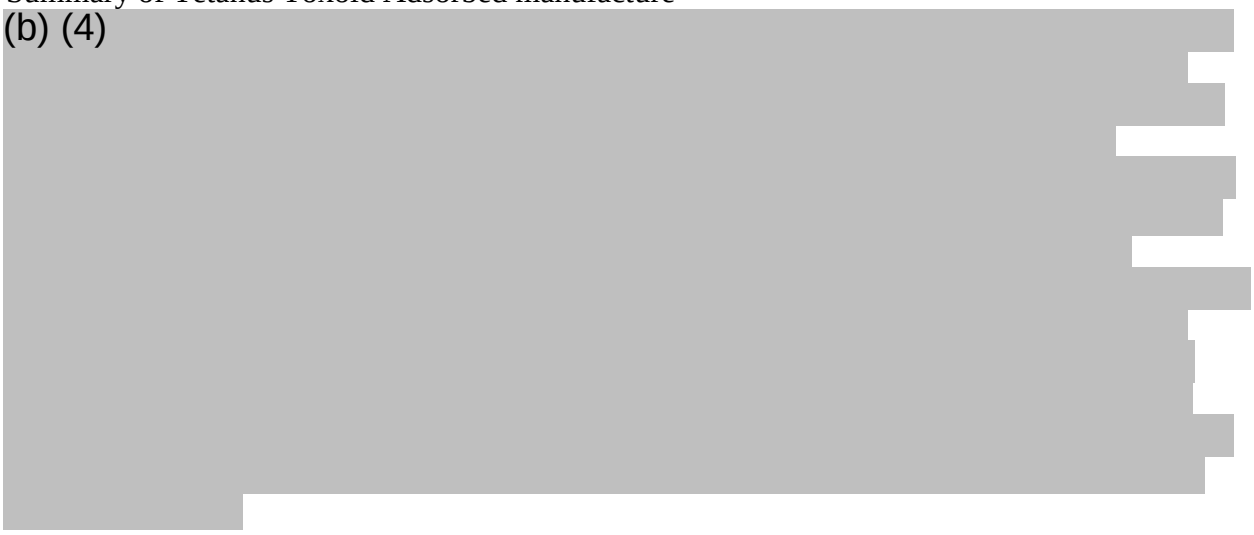
(b) (4)
Building (b) (4)

Building (b) (4)

In-process, release and stability testing for both toxoids

Summary of Tetanus Toxoid Adsorbed manufacture

(b) (4)



Summary of Diphtheria Toxoid Adsorbed manufacture

(b) (4)

Final Formulation

The final Quadracel formulation contains 5 Lf Tetanus Toxoid and 15 Lf Diphtheria Toxoid in a 0.5 mL dose. A review of stability data for Diphtheria Toxoid pre-adsorbed concentrates and Diphtheria Toxoid Adsorbed lots submitted with the Pentacel BLA met all testing requirements. Since Pentacel™ is formulated and filled under existing US license, the liquid vaccine formulation for Quadracel has been meeting all lot release and stability specifications for the past 10 years.

Recommendation

No CMC deficiencies have been found for the manufacture of Tetanus Toxoid adsorbed or Diphtheria Toxoid adsorbed. The manufacturing processes and process-controls for the manufacture of each component and for formulating the final product are acceptable. I recommend approval of this BLA.