FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

Date: February 23, 2015

From: Tod J. Merkel, LRSP/DBPAP

To: File for STN 125525/0

Through: Michael Schmitt, Chief, LRSP/DBPAP

Subject: 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 (Quadracel). CMC Review Pertussis Component

Sponsor: Sanofi Pasteur Limited, Toronto Canada

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EXECUTIVE SUMMARY

Sanofi Pasteur submitted this Biologics License Application (BLA) for "Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliomyelitis Vaccine" (Quadracel). The U.S. licensed vaccine Pentacel® is the combination of Haemophilus b Conjugate Vaccine (Tetanus Protein-Conjugate) reconstituted with Component Pertussis Vaccine Combined with Diphtheria and Tetanus Toxoids Adsorbed and Poliovirus Vaccine Inactivated (HCPDT-IPV). Pentacel® is distributed as two separately vialed components (ActHIB and HCPDT-IPV) that are combined at time of injection. The purpose of this BLA is to license the HCPDT-IPV component of Pentacel® as a stand-alone vaccine. The drug substances used to formulate Quadracel are the same as those used in the US-licensed Pentacel® vaccine. In addition, the drug product is formulated and filled in US-licensed facilities and the manufacturing process and release criteria for Quadracel final drug product are identical to those of the DTaP-IPV component of Pentacel. Because Quadracel is the HCPDT-IPV component of Pentacel® and no changes are being made at any step in the manufacture of the vaccine, the pertussis component CMC for Quadracel was reviewed at time of licensure of Pentacel®. I reviewed the manufacture of the pertussis component of Quadracel as part of the review of the Pentacel® BLA (STN:125145) including the seed banking, fermentation, purification and adsorption of the antigens to produce adsorbed bulk antigens, formulation of bulk drug substance, and filling of final drug product, in process controls, lot consistency and stability. No CMC deficiencies were identified for the manufacture of the PT component of Pentacel® and therefore, no CMC deficiencies were identified for the manufacture of the PT component or the formulation and filling of Quadracel. Pending reviews from the other disciplines, I recommend approval of this Biologics License Application.

REVIEW

Background:

Pentacel® is the combination of Haemophilus b Conjugate Vaccine (Tetanus Protein-Conjugate) reconstituted with Component Pertussis Vaccine Combined with Diphtheria and Tetanus Toxoids Adsorbed and Poliovirus Vaccine Inactivated (HCPDT-IPV). The HCPDT-IPV component is manufactured at Aventis Pasteur Limited and the PRP-T component is manufactured at Aventis Pasteur SA. The PRP-T Vaccine (filled and freeze-dried) is received at Aventis Pasteur Limited where it is labeled and co-packaged with labeled HCPDT-IPV Vaccine. Quadracel is the HCPDT-IPV component of Pentacel®. Because the manufacture of Quadracel is identical to the manufacture of Pentacel, the Pentacel BLA was cross-referenced for all aspects of pertussis component CMC. I reviewed the CMC sections of the Pentacel® BLA (STN:125145) including the seed banking, fermentation, purification and adsorption of the antigens to produce adsorbed bulk antigens, formulation of bulk drug substance, and filling of final drug product, in process controls, lot consistency and stability. No deficiencies were identified. In addition to the information provided in the original BLA for Pentacel®, we have approximately ten years of accumulated lot release data and formal stability results supporting the manufacture of the HCPDT-IPV component of Pentacel® (Quadracel).

Overview of Pertussis Component Manufacture:

The same adsorbed bulk pertussis antigens are used for the formulation of all of the licensed Sanofi Pasteur vaccines containing a pertussis component. These include Daptacel®, Pentacel®, and Adacel® and the subject of this BLA, Quadracel (See Table 1). The pertussis antigens

Pertussis Toxoid (PTx) and Filamentous Haemagglutinin (FHA) are purified from pertussis fermentation culture (b) (4) . Pertactin (PRN) and Fimbriae Types 2 and 3 (FIM) are purified from fermentation culture (b) (4) . PTx is detoxified with glutaraldehyde. FHA is treated with formaldehyde to detoxify residual PTx. Formaldehyde (rather than glutaraldehyde) is used for detoxification of residual PTx in FHA because it was determined that treatment of FHA with glutaraldehyde resulted in (b) (4) . Each of the component pertussis antigens, as well as diphtheria toxoid and tetanus toxoid, are adsorbed individually with aluminum phosphate and stored at (b) (4) , for the formulation of Adacel , Daptacel , Pentacel , and now Quadracel. No deficiencies were identified for the manufacture of the pertussis component bulk antigens.

The drug substances used to formulate the Quadracel final drug product are the same as those used in the US-licensed Pentacel® vaccine. In addition, the final drug product is formulated and filled in US-licensed facilities and the manufacturing process and release criteria for Quadracel final fills are identical to those of the DTaP-IPV component of Pentacel®.

Recommendation:
No CMC deficiencies were identified for the manufacture of the PT component of Pentacel® and therefore, no CMC deficiencies were identified for the manufacture of the PT component or the formulation and filling of Quadracel. Pending reviews from the other disciplines, I recommend approval of this Biologics License Application.