FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

Date: February 20, 2015

From: Juan L. Arciniega, 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 (Testing)

Sponsor: Sanofi Pasteur Limited (SPL), Toronto, Canada

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1 EXECUTIVE SUMMARY

The purpose of this Biologics License Application (BLA) is to license the HCPDT-IPV (DTaP-IPV) component of the US-licensed vaccine Pentacel® (indicated for active immunization against diphtheria, tetanus, pertussis, poliomyelitis and invasive disease due to Haemophilus influenza type b) as a stand-alone vaccine. HCPDT-IPV (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine) and two other US-licensed combination vaccines manufactured by SPL contain the same purified pertussis antigens used to formulate Quadracel. In addition, the drug products that constitute Pentacel® are formulated and filled in US-licensed facilities and the manufacturing process (including testing and release criteria for the pertussis drug substances) and pertussis testing and release criteria proposed for Quadracel final drug product are identical to those for the DTaP-IPV component of Pentacel®. Since Pentacel® licensing in 2008, CBER has released approximately (b) (4) lots of this vaccine using these or similar tests and criteria. Results of Pentacel® pertussis testing at release and as part of its formal stability testing program, support the suitability of the tests and specifications for the

HCPDT-IPV component of Pentacel® and therefore for Quadracel. Pending the opinion of other reviewers, I recommend approval of this BLA.

2 REVIEW

2.1 Background

SPL submitted this Biologics License Application (BLA) on March 24, 2014. DTaP-IPV (HCPDT-IPV; Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine) is the liquid portion of the US-licensed vaccine Pentacel® (STN 125145), which is used to reconstitute the lyophilized ActHIB (Haemophilus b Polysaccharide conjugated to Tetanus Toxoid; STN 103935). The two single-dose vials that constitute Pentacel® (ActHIB and HCPDT-IPV) are combined at the time of injection. The purpose of this BLA is to license the HCPDT-IPV component of Pentacel® as a stand-alone vaccine.

2.2 Review

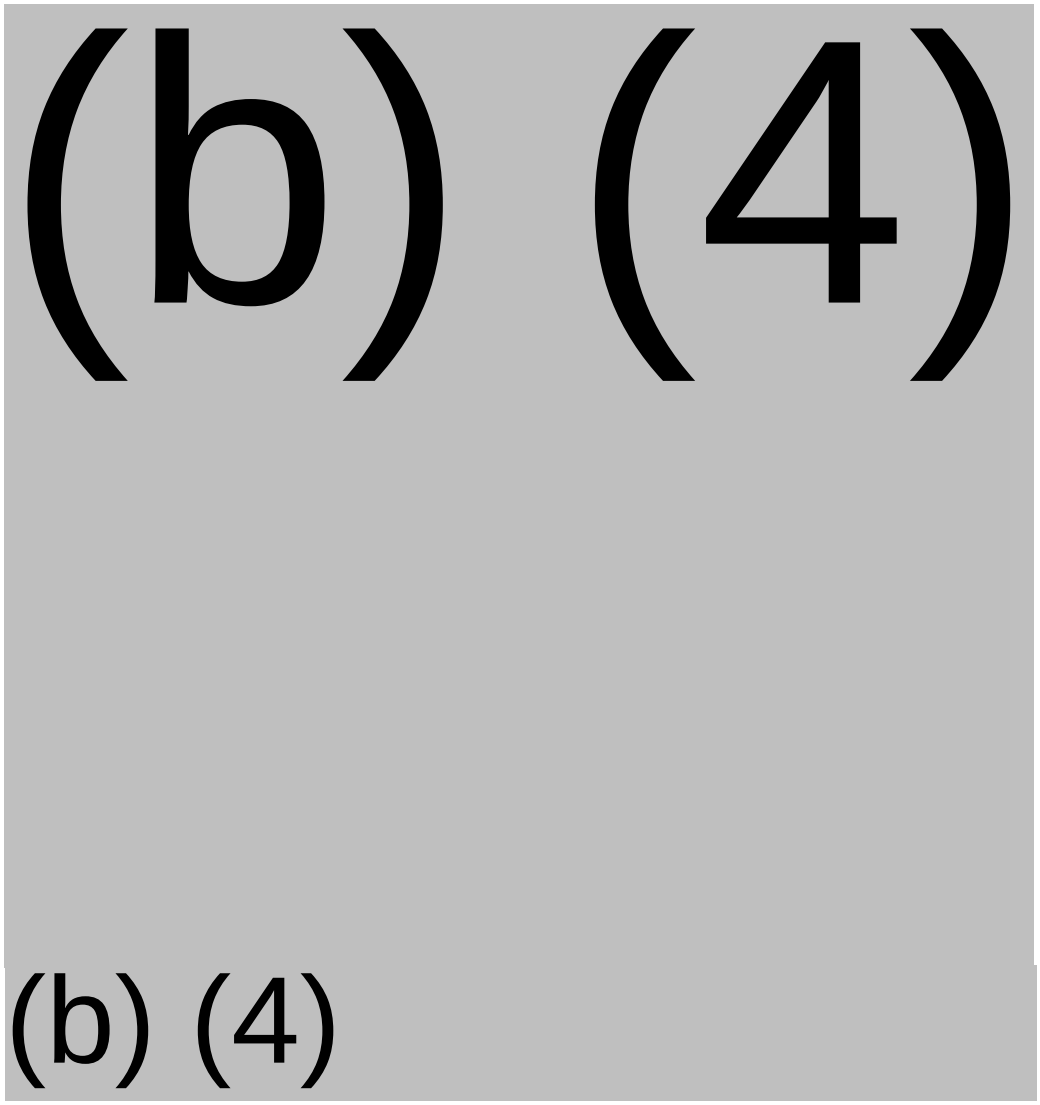
The purified pertussis antigens used to formulate Quadracel are present in other US-licensed combination vaccines manufactured by SPL [DTaP (DAPTACEL®) STN 103666, TdaP (Adacel®) STN 125111, and HCPDT-IPV (component of Pentacel® STN 125145]. In addition, the drug products that constitute Pentacel® are formulated and filled in US-licensed facilities and the manufacturing process (including testing of pertussis drug substances) and release criteria proposed for Quadracel final drug product are identical to those for the DTaP-IPV component of Pentacel®. DTaP-IPV and Quadracel are formulated to contain the following pertussis antigen concentrations per 0.5 ml dose: 20 µg Pertussis Toxoid (PT), 20 µg Filamentous Haemagglutinin (FHA), 5 µg Fimbriae Types 2 and 3 (FIM) and 3 µg Pertactin (PRN). Due to these reasons, and in accordance with CBER, SPL cross-references in Module 3 (Quality) of the Common Technical Document of the BLA of Quadracel the Pentacel® BLA (STN 125145/0), with the exception of the Lot Release Protocol (LRP).

In May, 2014, CBER asked SPL to clarify the cross-referencing to the Pentacel® file (STN: 125145/0), because there have been approved modifications to the CMC in the Pentacel file (including test methods and specifications) that are not included in the original BLA application for Pentacel®

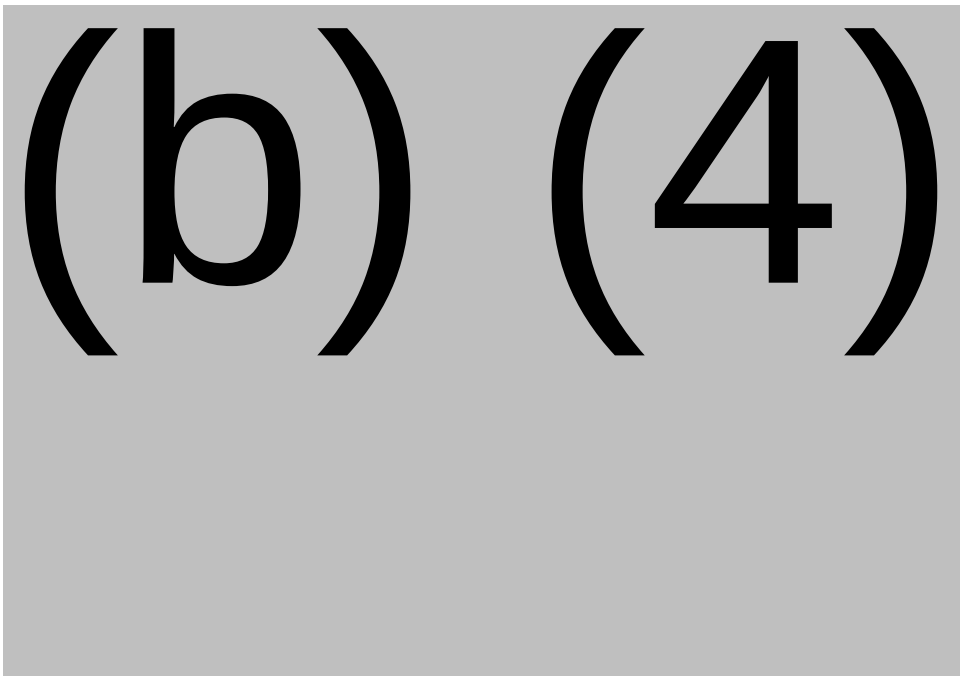
On November 13, 2014, SPL clarified its intention of cross-referencing the whole Pentacel® file (STN 125145), which is applicable in its entirety to Quadracel, including not only the original BLA (125145/0), but all Amendments during licensure, and all subsequent CMC supplements and Annual Reports.

The following tests and specifications for the pertussis drug substances and the tests and specifications for the pertussis component in HCPDT-IPV (DTaP-IPV) as final bulk of Pentacel® are identical to the proposed tests and specifications included in the original Quadracel LRP:

Tests and Specifications on Pertussis Drug Substances



DTaP-IPV Final Bulk Pertussis Testing



On September 15, 2014, SPL submitted to the Quadracel file an amended and annotated draft Pentacel® LRP, in which they requested:

1. To remove from the LRP the (b) (4) reports containing detailed results for the pertussis antigens, which have been submitted to date for Pentacel® (e.g, Figures 9 and 10 for PTx in the original Quadracel LRP), and to provide instead only an overall summary of data results; and

2. To remove from the LRP the detailed data reports that have been submitted to date for Pentacel® (e.g. Figures 1-4 for Stage 1 in the original Quadracel LRP), for the Mouse Immunogenicity test performed on drug product, and to provide instead only the overall summary of results.

On December 3, 2014, I communicated to SPL my approval of the following changes to the pertussis section of the LRP for Pentacel®, pending CBER's sample custodian concurrence:

1. The removal of the (b) (4) reports for the pertussis antigens, and the inclusion of only an overall summary of data results.

2. The removal of the data reports for the acellular pertussis (aP) vaccine mouse immunogenicity (potency) test, and the inclusion of only the overall summary of results,

As requested for Pentacel® by SPL on September 15, 2014. Because of the cross-referencing between the Pentacel® and the Quadracel files, these changes to the LRP are also approvable for Quadracel.

In addition to the approval of the pertussis testing and specifications provided in the original BLA for Pentacel®, its supplements and annual reports, CBER has released approximately (b) (4) lots of this vaccine since its licensing in 2008.

Results of Pentacel® testing at release and as part of its stability testing program support the suitability of the pertussis tests and specifications for the HCPDT-IPV component of Pentacel® and therefore for Quadracel.

3 RECOMMENDATION

Pending the opinion of other reviewers, I recommend approval of this Biologics License Application.