Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: March 10, 2015

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STN: 125525/0 (Quadracel), 125525/0.2, 125525/0.3, 125525/0.5, and 125525/0.6

Submission Type: Original BLA
Submission Date: March 24, 2014
Action Date: March 24, 2015

Products: Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliovirus (DTaP-IPV) Vaccine (Quadracel)

Sponsor: Sanofi Pasteur Limited

Subject: Registration of the DTaP-IPV vaccine in the US as a 5th dose booster in children 4 to 6 years of age**:** Review of the Lot Release Protocol (LRP) for the Poliovirus component and review of the assay for quantitation of Poliovirus antibodies

Summary

Quadracel is a combination of diphtheria and tetanus toxoids adsorbed, acellular pertussis (PT, FHA, PRN, and FIM types 2 and 3) adsorbed, and inactivated Poliovirus (DTaP-IPV). Quadracel is a component of Pentacel, which additionally includes a vial of lyophilized Hib vaccine (PRP-T). Pentacel has been approved for use in the US since June 2008 and in this submission, the sponsor seeks to license Quadracel separately (i.e., as a stand-alone product). The drug substances (including the poliovirus component) used to manufacture and formulate Quadracel are the same as those used in Pentacel. In addition, Quadracel is formulated and filled in US-licensed facilities and the release criteria for Quadracel final fills are identical to those of the DTaP-IPV component of Pentacel. Thus,

as per written agreement from CBER (05 February 2014), the Quadracel BLA references the Pentacel BLA (125145/0) for Module 3 (Quality) except for section 3.2.P.5.4 which contains the Lot Release Protocol (LRP) for DTaP-IPV, Module 4 (Non-Clinical Study reports), and Module 5 (Clinical Study Reports). Module 5 references Study 494-01 from the Pentacel BLA to demonstrate IPV lot to lot consistency, but does include Poliovirus immunogenicity and safety data in this submission (Study M5I02) to support equivalence and licensure of DTaP-IPV for administration as a 5th dose booster in US children 4 to 6 years of age. The (b) (4), performed at Sanofi Pasteur Inc., by (b) (4) was used to quantify anti-poliovirus antibody levels in human serum in study M5I02. The test was performed according to protocol Q_0278720 (Poliovirus Antibody Determination by (b) (4) and was validated in December 2005 (detailed in Q_0254201, Validation Report for SWI J001656, "Poliovirus Antibody Determination by (b) (4)") prior to use in the testing of clinical samples. The validation studies showed that the Poliovirus (b) (4) is valid and suitable for its intended use to measure the levels of neutralizing antibodies to Poliovirus types 1, 2, and 3 in human serum.

Note: Although an amended version of the Pentacel LRP was submitted with this application, following a CBER review (see below) of the proposed changes and discussion with the sponsor, this protocol was withdrawn and replaced (February 3rd 2015; STN 125525/0.6) with the currently approved LRP under the Pentacel file. CBER's outstanding concerns with regard to the modified LRP will be addressed under STN 125145 (Pentacel) prior to implementation of the protocol under STN 125525 (Quadracel).

Review

All aspects of the manufacture including cell banks, poliovirus seed stocks, virus propagation, virus harvest, inactivation of the poliovirus monovalents, pooling of the monovalent concentrates, formulation of the trivalent concentrates, stability profiles of the drug substance and release specifications of the poliovirus component of Quadracel are identical to the US licensed Pentacel vaccine. The final Quadracel formulation containing 40, 8, and (b) (4) D antigen units of poliovirus types 1, 2, and 3 respectively in a 0.5 mL dose is identical to Pentacel. All CMC data relevant to the poliovirus component have previously been reviewed and approved by CBER under the Pentacel file and no additional CMC data were submitted to STN 125525. As per the written agreement with CBER, this BLA references the approved Pentacel BLA except for the LRP (Section 3.2.P.5.4, Module 3), Clinical Study M5I02 and validated serology assays (Module 5) to support the licensure of Quadracel for administration as a 5th dose booster in US children 4 to 6 years of age. This review is limited to the section of the LRP detailing the Poliovirus tests and the serology assay (b) (4) used to quantify anti-poliovirus antibody levels in human serum.

LRP: Poliovirus testing

With regard to the Poliovirus tests, the LRP submitted in the current supplement for Quadracel is identical to the approved LRP used under the Pentacel license except for the changes summarized below:

1. Poliovirus Monovalent sections:
   A) Changes in terminology (Test On/Date Test On/Date Test Started changed to On Test Date and Test Off/Date Test Off/Date Test Completed changed to Off Test Date), re-wording of some IPV stages (Poliovirus Inactivated Monovalent Type 1/2/3 changed to

Poliovirus Monovalent Inactivated Type 1/2/3 and Purified Poliovirus Monovalent Type 1/2/3 changed to Poliovirus Monovalent Purified Type 1/2/3) and re-ordering of the information presented.

B) Tables 8 [Mycoplasma Testing (b) (4)] and 14 [Mycoplasma Testing (b) (4)] for Poliovirus Types 1 and 3 have been reconfigured as per CCR #2103994 wherein (b) (4) are not stated in the LRP and it is unclear if these changes have been validated. Note, the mycoplasma tables for Type 2 remain the same as those contained in the Pentacel file.

2. Poliovirus Trivalent Concentrate section:
   Changes in terminology, re-wording of some IPV stages, re-ordering of the information presented and updates of figures and tables. Of note, Figure 1 and Table 2 in this section list use of a (b) (4) ; STN 125145/38) and a new MRC-5 Lot ((b) (4) ; STN 125145/105). Additionally, in Table 2 the control cells are not identified as control cells, but only as "MRC-5 cells."

3. DTaP-IPV Final Bulk section:
   The standard used in the (b) (4) Test (Table 11) is now referred to as the "reference vaccine (Positive Control)". In addition, the table now includes an expiry date for the reference vaccine and (b) (4) .

Note, the same changes were also submitted by the applicant for the Pentacel LRP and are currently under review. Please see further details under "Comments relayed to the sponsor" and "Response from the sponsor."

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Comments relayed to the sponsor (August 29, 2014)

1. With regard to the Poliovirus (b) (4), please provide data demonstrating assay stability (performance) since the last validation.

2. With regard to the poliovirus component of the Lot Release Protocol, please confirm whether the changes to Tables 8 [Mycoplasma Testing (b) (4)] and 14 [Mycoplasma Testing (b) (4)] have been approved by CBER and if so reference the appropriate submission.

3. The following Information Requests pertaining to the poliovirus component of the Lot Release Protocol were previously relayed on June 18, 2014 for the Pentacel product. These also pertain to the Quadracel product. Please respond to these requests to both files.

A) In Table 1 (b) (4)

B) Please clearly define Off Test Date in the LRP. In the past, this date has corresponded to either date of test completion or date of sign off / approval.
C) In Table 2 "Poliovirus Trivalent Concentrate Lot Genealogy", use of the terminology MRC-5 cells is ambiguous. Please revise the terminology to "MRC-5 Control Cells".
D) In Table 11 "Poliovirus Vaccine Inactivated (b) (4)", use of the terminology "Reference Vaccine (Positive Control)" is inappropriate. Please consider reverting this terminology to "Relative to Standard".
E) Tables 8 [Mycoplasma Testing (b) (4)] and 14 [Mycoplasma Testing (b) (4)] have not been reconfigured for poliovirus Type 2. Please explain.

Response from the sponsor (STN 125525/0.3; September 15, 2014)

1. Document RED_00073615 (STN 125525/0.2) provides data demonstrating the long term performance of the Poliovirus (b) (4) from January 2005 through March 2014 thorough analysis of historical results of a) the serotype-specific TCID50 and b) the positive internal quality control (IQC) reference ratio.
   The TCID50 for poliovirus type 1 and poliovirus type 2 have generally performed within the acceptable range of (b) (4) TCID50 from January 2005 to March 2014. However, the TCID50 for poliovirus type 3 lot (b) (4) had a trend outside of the acceptable range from June 2013 to January 2014 whereby more than half of tests failed due to

TCID50 falling out of range on the high end (i.e., TCID50 (b) (4)). The root cause of the TCID50 shift of (b) (4)

Poliovirus type 3 lot (b) (4) has been removed from use and a new poliovirus type 3 lot (b) (4) was prepared and qualified for use according to Instruction Q_0521837, *Handling, Storage and Qualification of Poliovirus Serotype 1, 2 & 3 for Use in Instruction Q 0278720, Poliovirus Antibody Determination by* (b) (4) (7.6).
(b) (4)

Note, the IQC reference ratio assay validity criterion and corresponding acceptance range will be phased out of the current assay protocol (Instruction Q 0278720, *Poliovirus Antibody Determination by* (b) (4)), and will be replaced with the (b) (4) acceptance range. The acceptance range of the current lot of (b) (4) will be set for each poliovirus serotype and will be included as a new assay validity criterion to monitor assay stability and reproducibility. To support this new assay validity criterion, Figures 10 through 12 (control charts for serotype-specific titers for (b) (4)) are included in Document RED_00073615 and demonstrate consistency of the IQC titer for each of the poliovirus serotypes.

2. An updated version of the Lot Release Protocol was submitted via email to CBER, in response to the 18 June Information Request, on 03 September 2014 to the Pentacel BLA (STN BL 125145). Final approval of this revised document is pending. Once approved, the relevant sections for the diphtheria, tetanus, pertussis, and poliovirus components of Pentacel will be filed to Quadracel STN 125525, including the changes to Table 8 regarding mycoplasma testing.

3. A) The calculated D-Antigen concentration is derived from the D-Antigen value at the earlier (b) (4) stage. The testing procedure for the D-Antigen at (b) (4) was revised to test (b) (4)

. This change was approved by CBER on 27 March 2014 (STN BL 125145/297 and BL 103940/5096: Approval of request to (b) (4)

B) A new section "Notes for Reviewers" has been added on Page 7 of 46. This section will include the following:
"Date of Test" refers to the "Date Test was reviewed and authorized" in LIMS by Quality Control.
"On Test Date" refers to the "Date Test was started"
"Off Test Date" refers to the "Date Test was completed"
This section will also capture any special notes required for reviewers' attention and review of data.

C) As suggested by the reviewer, MRC-5 Cells will be referred to as "Control MRC-5 Cells" (Page 10 of 17).

D) The "Positive Control" for Poliovirus Vaccine (b) (4) Test is updated to "Standard Lot Number" (Page 23 of 46). The "Reference expiry date" entry field is also deleted (Page 23 of 46).

E) This was missed in the proposed draft by the sponsor. The Mycoplasma testing of (b) (4) (Page 15 of 18) and (b) (4) (Page 18 of 18) for the Poliovirus Monovalent Inactivated Type 2 is updated to align with Types 1 and 3 IPV Monovalent templates.

Comments relayed to the sponsor (October 31, 2014 and November 10, 2014)

1. We note that the IQC reference ratio assay validity criterion will be removed from the Poliovirus (b) (4) protocol (Instruction Q_0278720) and replaced with an IQC titer acceptance range (125525/0.2; RED_00073615). Please confirm that supportive data will be submitted for review prior to the institution of this change.

2. Please state the actual (i.e. experimentally determined) and the calculated D-antigen value for each poliovirus monovalent at the (b) (4) in Table 1 "Poliovirus Monovalent Inactivated Testing" (Page 3/18 for each poliovirus monovalent in the updated lot release protocol).

3. In Table 11 "Poliovirus Vaccine Inactivated (b) (4) " (Page 23 of 46) of the updated lot release protocol, please amend "Acceptance Criteria: (b) (4)" to "Acceptance Criteria: (b) (4) for each Poliovirus Type relative to Standard Lot". In addition please include the expiry date for the Standard Lot in Table 11.

Response from the sponsor (STN 125525/0.5; November 27, 2014)

1. Technical report RED 00073462 describes the qualification of positive control lot (b) (4) with set reference titer range limits for each Poliovirus type for use in the Poliovirus (b) (4) . Technical report RED_00077223 describes the qualification of positive control lot (b) (4) with set reference titer range limits for each Poliovirus type as well as the qualification of negative control lo (b) (4).

   Qualification of positive control lot(b) (4)
   (b) (4)

(b) (4)

(b) (4)

2. Table 1 "Poliovirus Monovalent Inactivated Testing" (Page 3/18 for each poliovirus monovalent in the updated lot release protocol) states the calculated D-antigen concentration while a footnote to Table 1 now states the experimentally determined D-antigen value.

3. Table 11 "Poliovirus Vaccine Inactivated (b) (4) " (Page 23 of 46) of the updated lot release protocol has been amended to include the expiry date for the Standard Lot and states "Acceptance Criteria: (b) (4) for each Poliovirus Type relative to Standard Lot".

Comments and Recommendation

The manufacture, formulation and dosage of the poliovirus component for Quadracel is identical to the US licensed Pentacel vaccine. The CMC data for poliovirus have previously been reviewed and approved under the Pentacel file and no additional CMC data were submitted to this file.

Validation, demonstration of assay stability, qualification of the three IQC and implementation of the IQC titer acceptance range for use in the Poliovirus (b) (4) are appropriate. Additionally, all concerns regarding the poliovirus component of the LRP, except those relevant to the mycoplasma test, have been addressed. The sponsor has yet to adequately address the changes to the mycoplasma test (performed on (b) (4) and poliovirus (b) (4)) and despite an additional information request from DBSQC (November 4, 2014) seeking clarification on the changes to the assay, an assessment demonstrating equivalency between the current and proposed assay methodology has not been provided.

Note, in order to expedite the review of this submission, Sanofi Pasteur submitted (February 3rd 2015; STN 125525/0.6) the Pentacel-approved LRP (currently in use for the DTaP-IPV component of Pentacel; STN 125145) to the Quadracel file. CBER's outstanding concerns with regard to the mycoplasma test will be addressed under STN 125145 (Pentacel) prior to implementation of the modified LRP under STN 125525 (Quadracel).

Given that all concerns regarding poliovirus have been adequately addressed by the sponsor (i.e. appropriate validation of the poliovirus (b) (4) and use of the LRP approved under the Pentacel license), I recommend approval of Quadracel for use as a 5th dose booster in children 4 to 6 years of age.