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

Memorandum

Date: July 2, 2014

From: Freyja Lynn, CSO, DBPAP, Committee Member

To: STN 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

Through: Jay Slater, Director, DBPAP

Subject: Complete Review Memo
Clinical serology data, study Pivotal Study M5I02. Pertussis responses
Serologic assay performance review, pertussis

Firm: Sanofi Pasteur

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 pivotal data to support licensure come from study M5I02 which demonstrated the noninferiority of their DTaP-IPV when compared to concomitantly administered DAPTACEL and IPOL. This memo reviews the data submitted to support the performance of the clinical serology assays to quantitate antibodies against pertussis antigens. Also reviewed are the anti-pertussis antibody data submitted in the clinical study report.

The assays to quantitate antibody against pertussis antigens were validated in 2006. The validations included sufficient data on the precision and dilutional linearity to support the use of the assays for clinical studies that use threshold, fold rise or geometric mean antibody concentrations as endpoints. The lower limits of quantitation appear appropriately set. Stability data tracking the control sample values over time support the continued performance of the assay since validation.

The data in the clinical data are consistent with adequate performance of the assays and demonstrate that the DTaP-IPV is noninferior to DAPTACEL and IPOL administered concomitantly with regard to the responses to the pertussis antigens.

Review

ELISAs for the quantitation of IgG against pertussis antigens

The following documents were submitted in support of the performance of the assays to quantitate responses to the pertussis antigens.

Q_0279116, ELISA Method for the Detection of Human Antibodies to PT Antigen
Q_0254868, Validation Report for SWI J003829, "ELISA Method for the Determination of Human Antibodies to Pertussis Toxin (PT) Antigen" Version 4.0
Q_0279083, ELISA Method for the Detection of Human Antibodies to Filamentous Haemagglutinin Antigen.
Q_0254615, Validation Report for SWI J003792, "ELISA Method for the Detection of Human Antibodies to Filamentous Haemagglutinin" Version 2.0
Q_0279130, ELISA Method for Detection of Human Antibodies to Fimbrial Agglutinogens (2+3) Antigen.
Q_0254614, Validation Report for SWI J003847, "ELISA Method for the Detection of Human Antibodies to Fimbrial Agglutinogens (2+3) Antigen" Version 2.0
Q_0279131, ELISA Method for Detection of Human Antibodies to Pertactin ((b) (4)) Antigen
Q_0254611, Validation Report for SWI J003848, "ELISA Method for the Detection of Human Antibodies to Pertactin ((b) (4)) Antigen" Version 2.0

The methods for each assay were similar. Plates were coated with the appropriate purified protein, then the reference, control and test sera are added. The antibody was directly proportional to the binding of the enzyme conjugated anti –human IgG and signal of the relevant substrate. Samples were tested at (b) (4) .

Validations were performed in 2006. (b) (4)

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(b) (4)

Summary

The data support adequate performance parameters for the use of this assay to generate data for clinical studies with threshold, fold rise and geometric mean endpoints. Minor issues with the validation reports were noted during review of these assays for IND 14668 with comments sent to the sponsor and adequate responses received 15 November 2013 (amendment 15).

Pivotal Study M5I02, Safety and Immunogenicity of DTaP-IPV (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliovirus Vaccine) Compared to DAPTACEL (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) + IPOL (Poliovirus Vaccine Inactivated) as the 5th Dose in Children 4 to 6 Years of Age.

Subjects in Group 1 received 3 vaccines concomitantly: a dose of DTaP-IPV vaccine, a dose of MMR vaccine, and a dose of V vaccine.
Subjects in Group 2 received 4 vaccines concomitantly: a dose of DAPTACEL vaccine, a dose of IPOL vaccine (DAPTACEL + IPOL), a dose of MMR vaccine, and a dose of V vaccine.
Subjects in Group 3 received up to 3 vaccines concomitantly: a dose of DTaP-IPV with or without a dose of MMR and V vaccine(s).
Subjects in Group 4 received up to 4 vaccines concomitantly: a dose of DAPTACEL vaccine, a dose of IPOL vaccine, with or without a dose of MMR vaccine, and a dose of V vaccine.

Primary Objectives (Immunogenicity)

- To compare the pertussis (pertussis toxoid [PT], filamentous aemagglutinin [FHA], pertactin [PRN], and fimbriae types 2 and 3 [FIM]) booster responses and geometric mean concentrations (GMCs) (as measured by enzyme-linked immunosorbent assay [ELISA]) following DTaP-IPV vaccination (Group 1) to those elicited following DAPTACEL + IPOL vaccination (Group 2) when administered as a 5th dose
- To compare the diphtheria and tetanus booster responses and GMCs (as measured by neutralizing assay and ELISA, respectively) following DTaP-IPV vaccination (Group 1) with those elicited following DAPTACEL + IPOL vaccinations (Group 2) when administered as a 5th dose
- To compare the IPV booster responses and geometric mean titers (GMTs) (as measured by neutralizing assay) following DTaP-IPV vaccination (Group 1) with those elicited following DAPTACEL + IPOL vaccinations (Group 2) when administered as either a 4th or 5th dose.

Sera were collected pre and approximately 28 days post immunization.

Only the data related to the first objective (responses to pertussis antigens) are reviewed in this memo. The primary hypothesis was that anti-pertussis booster response rates and geometric mean concentrations (GMCs) for pertussis antigens (PT, FHA, PRN, and FIM) would be non-inferior in subjects who receive DTaP-IPV as a 5th dose when compared to the booster response rates of subjects who receive DAPTACEL + IPOL as a 5th dose. Non-inferiority of DTaP-IPV was demonstrated if the lower limits of the 2-sided 95% CIs of the difference (DTaP-IPV minus DAPTACEL + IPOL) in post-vaccination booster response rates for all pertussis antigens between groups were > -10%. For the analysis using GMCs, non-inferiority of DTaP-IPV was demonstrated if the lower limits of the 2-sided 95% CIs of the ratio

(DTaP-IPV / DAPTACEL + IPOL) in post-vaccination GMCs for all pertussis antigens between groups were > 2/3.

For purposes of computation, values less than the LLOQ were imputed to ½ the LLOQ. Booster response rate for pertussis (PT, FHA, PRN, and FIM) was defined as: subjects with a pre-vaccination antibody concentration < LLOQ, achieving a post-vaccination level ≥ 4X LLOQ; subjects with a pre-vaccination antibody concentration ≥ LLOQ but < 4X LLOQ, achieving a 4-fold rise rate of post-vaccination over the prevaccination antibody concentration; subjects with a pre-vaccination antibody concentration ≥ 4X LLOQ, achieving a 2-fold response.

The results for response rates are presented in the table below (from Table 5.1 of the clinical study report). Number of subjects in each group ranged from 247 to 254. Subjects receiving DTaP-IPV had higher response rates against all pertussis antigens than those receiving DAPTACEL + IPOL.

Antigen	% responders DTaP-IPV	% responders DAPTACEL + IPOL	95% CI of difference in rates
PT	95.2	89.9	0.7 – 10.2
FHA	94.9	87.5	2.5 – 12.5
PRN	96.9	93.1	-0.2 – 7.9
FIM	97.2	92.4	0.9 – 9.1

The results for GMCs are presented below (from Tables 5.2 and 5.3 of the clinical study report). Values are ELISA Units/ml. Number of subjects in each group ranged from 248 to 263. Prevaccination GMCs were comparable between groups. Post vaccination GMCs in subjects receiving DTaP-IPV were higher against all pertussis antigens than in those receiving DAPTACEL + IPOL.

Antigen	DTaP-IPV (95% CI)	DAPTACEL + IPOL (95% CI)	GMC Ratio (95% CI)
PT	121 (108-134)	61.3 (54.5-68.9)	1.97 (1.68-2.31)
FHA	123 (108-141)	79.0 (69.3-90.0)	1.56 (1.30-1.88)
PRN	283 (252-317)	187 (164-214)	1.51 (1.27-1.79)
FIM	506 (448-571)	379 (331-433)	1.33 (1.12-1.60)

The reverse cumulative distribution curves for the antibodies to all four pertussis antigens showed that the curves for the subjects who received DTaP-IPV were the same shape as the curves for the subjects who received DAPTACEL + IPOL but shifted to the right, indicating an overall generally higher response in the subjects who received DTaP-IPV.

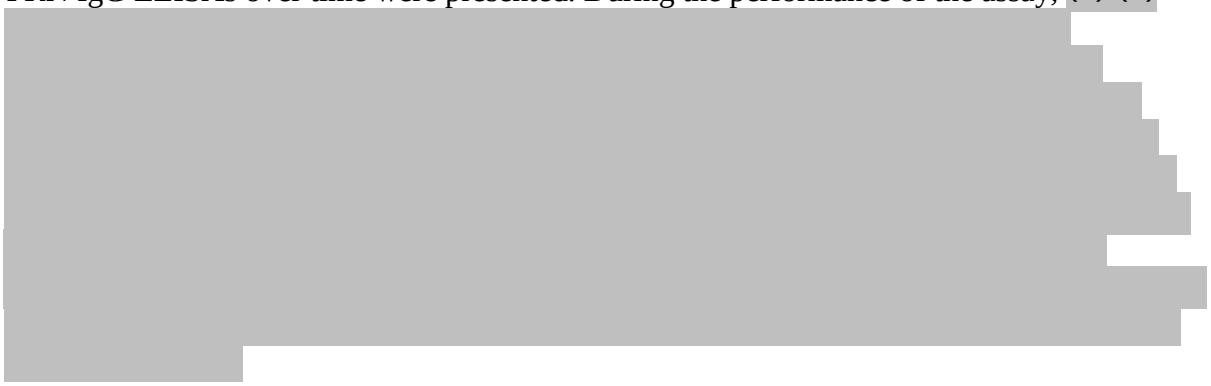
Review of all data, including the line listings, show no aberrant results.

To confirm that the assays used to generate the data used in the study were performing adequately and that no data were inappropriately excluded from the analysis, the following information requests were sent to the sponsor on 12 May 2014.

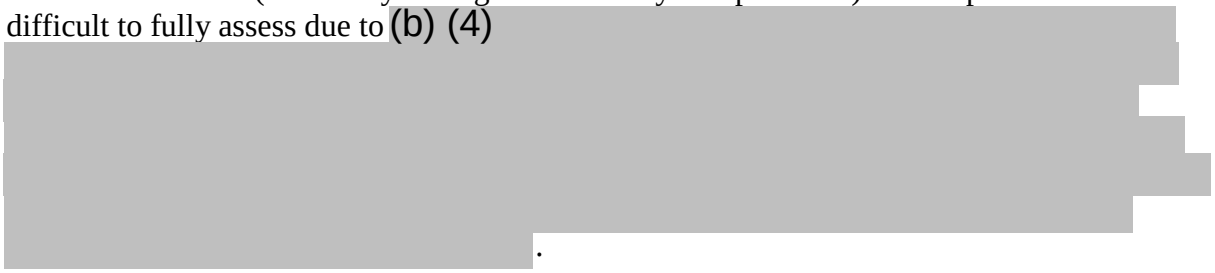
1. Please provide data to support the stability of the performance of the immunoassays used to assess responses to diphtheria, tetanus and pertussis from the time of validation to the analysis of samples in in study M5I02.

2. If you retested samples in your immunologic assays and replaced specific data points in study M5I02, please provide a summary of retesting either as part of the Clinical Study Report or separately. In this summary, we request you include a listing of the values replaced during data cleaning, reasons for sample retesting, and an assessment of the impact of the retesting and replacement of values.

In response to question 1, Sanofi submitted RED_00073695: Demonstration of the Long-Term Performance of the Anti- Pertussis IgG ELISAs using Plots of Control Results, Version 2.0, 13 Jun 2013. Plots of the high control for the anti-PT, anti-FHA, anti-FIM 2+3, and anti-PRN IgG ELISAs over time were presented. During the performance of the assay, (b) (4)



The data support the stability of the assay over time in which the clinical samples from Study M5I02 were tested (laboratory testing dates January to April 2012) but the performance is difficult to fully assess due to (b) (4)



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In response to question 2, Sanofi submitted RED_00069240, Biological Validation: M5I02 Tetanus ELISA, Diphtheria (b) (4), Polio (b) (4) (Types 1, 2 & 3) and Pertussis ELISAs (PRN, FHA, FIM, PT), Version 2, 19 Jun 2014. The report indicates that the expected number of samples was repeated in the pertussis assays based on the statistical analysis. Very few data points were replaced based on the retesting. However, one sample identified for retesting could not be tested due to QNS. The value for this sample was removed from the analysis. While only one case of this practice was seen in the data from the pertussis assays, this

practice should be discouraged. If samples identified cannot be retested, the original value should be retained in the analysis to prevent the introduction of bias.

Recommendation

Regarding the assays used to quantitate responses to the pertussis antigens, the validation reports and assay stability data indicate that the assays have the appropriate performance parameters for use in the clinical studies for this BLA. The clinical data from Study M5I02 appear to be consistent with the expected assay performance and support the noninferiority of the DTaP-IPV responses to the DAPTACEL + IPOL responses. I recommend approval of this BLA.