



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

Memorandum

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To Julienne Vaillancourt, Chair, BLA Review Committee

File BLA 125324

Product Prevnar 13™ [Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM197 Protein)]

Subject STN 125324: Review of serology methodology used for Prevnar 13™, and concomitantly administered Haemophilus influenzae type B and Meningococcal type C vaccines.

Reference: List of BLA submission(s) reviewed.

- 1) 5.3.1.4 -13V Pn II EIA IgG –(b)(4)--Summary of the validation of pneumococcal enzyme linked immunosorbent assays (Pnelisas) for pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18V, 19A, 19F, and 23F to support serological testing of pneumococcal polysaccharide.
- 2) 5.3.1.4- 13V Pn OPA HL-60 - Summary of the validation of Streptococcus pneumoniae opsanophagocytic assay (Pnopa) for serotypes Pn1, Pn3, Pn4, Pn5, Pn6A, Pn6B, Pn7F, Pn9V, Pn14, Pn18V, Pn19A, Pn19F, and Pn23F.
- 3) 5.3.1.4- Hib EIA IgG-Summary of the validation of method of the Haemophilus influenzae (Hib) ELISA.
- 4) 5.3.1.4- Mening C SBA- Summary of the validation of the Neisseria meningitidis serogroup C serum bactericidal assay.
- 5) 5.3.1.4- Opsanophagocytic assay related amendment.
Amendment 125324/08 (submitted on May 1 2009).
 - MVP-1001 OPA Validation protocol
 - MVP-1018 OPA Validation protocol –Test Range Extension Serotypes 1, 6A, and 23F.
 - VR-TM-10028 (TM-3030) OPA Test Method.
 - RPT-71821 Validation Report for Pn1 OPA.
 - RPT-71748 Validation Report for Pn3 OPA.
 - RPT-71822 Validation Report for Pn4 OPA.

- RPT-71823 Validation Report for Pn5 OPA.
 - RPT-71824 Validation Report for Pn6A OPA.
 - RPT-71825 Validation Report for Pn6B OPA.
 - RPT-71826 Validation Report for Pn7F OPA.
 - RPT-71827 Validation Report for Pn9V OPA.
 - RPT-71828 Validation Report for Pn14 OPA.
 - RPT-71829 Validation Report for Pn18C OPA.
 - RPT-71830 Validation Report for Pn19A OPA.
 - RPT-71831 Validation Report for Pn19F OPA.
 - RPT-71833 Validation Report for Pn23F OPA.
 - RPT-73343 Validation Report for Range Extension of Pn1 OPA.
 - RPT-73344 Validation Report for Range Extension of Pn6A OPA.
 - RPT-73345 Validation Report for Range Extension of Pn23F OPA.
- 6) 4.2.3.2.1- --(b)(4)--- ELISA (----(b)(4)-----) used to measure IgG antibodies as part of --(b)(4)--- toxicity assay.
- Amendment 125324/09 (submitted on May 5, 2009).*
- RPT-73286 Qualification Report for PnPs ---(b)(4)--- Assay.

Overview:

The Diphtheria CRM197 Protein conjugated 13 valent pneumococcal vaccine contains the thirteen capsular polysaccharides from the serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. The vaccine is intended to prevent Invasive Pneumococcal Disease (IPD) and acute otitis media due (AOM) caused by strains carrying the capsular polysaccharide serotypes included in the 13 valent vaccine. Correlation between the serum antibody levels and protection against IPD and AOM has been established during the clinical studies conducted with the approved 7 valent vaccine, Prevnar®. As a result, serum antibody levels, measured in ELISA, and the biological activity of these antibodies, measured in opsonophagocytic assay (OPA) are used in clinical efficacy studies.

Serum response to concomitantly administered *Haemophilus influenzae* type b vaccines and the meningococcal type C vaccines are also assayed. An ELISA is used to measure the serum antibody levels against the vaccine antigen *H. influenzae* type b capsular polysaccharide polyribosyl ribitol phosphate (PRP) and a serum bactericidal assay (SBA) is used to measure the biological activity of serum antibodies against meningococcal type C strains.

Review of individual assays:

1) Assays used to assess response to 13vPnC vaccine.

1.1 *Pneumococcal ELISA:*

1.1.1 ELISA Principal and Method:

13vPn ELISA measures IgG antibodies against 13 vaccine serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) in human serum. This ELISA is based on the previously

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Clinical trials where Pneumococcal ELISA is used.

- 5.3.5.1 Study-003 - Double-Blind 13vPnC vs 7vPnC Trial in Healthy Children
- 5.3.5.1 Study-004 - CSR-69238- Randomized, Double-Blind Trial Comparing 13vPnC in Healthy Infants in the United States.
- 5.3.5.1 Study-009 - Randomized, Double-Blind 13vPnC Trial with and without Polysorbate 80 in Healthy Children.
- 5.3.5.1 Study-3007 - Randomized, Double-Blind 13vPnC Trial with a Meningococcal C Conjugate Vaccine and Other Routine Pediatric Vaccinations in Spain.
- 5.3.5.1 Study-006 - Randomized, Double-Blind Trial Comparing 13vPnC to 7vPnC in Healthy Pediatric Subjects in Germany.
- 5.3.5.1 Study-500 - Randomized, Double-Blind 13vPnC Trial with Routine Pediatric Vaccination in Italy.
- 5.3.5.1 Study-501 - Randomized, Double-Blind 13vPnC Trial with Routine Pediatric Vaccination in Spain
- 5.3.5.1 Study-3008 - Randomized, Double-Blind 13vPnC Trial in Healthy Infants with Routine Pediatric Vaccinations in Canada.
- 5.3.5.1 Study-007 - Randomized, Active-Controlled, Double-Blind Trial Evaluating the Safety, Tolerability, and Immunogenicity in Healthy Infants Given With Routine Pediatric Vaccinations in the United Kingdom".
- 5.3.5.1 Study-008 - Randomized, Active-Controlled, Double-Blind, Trial Evaluating the Safety, Tolerability, and Immunogenicity in Healthy Infants Given With Routine Pediatric Vaccination in France.
- 5.3.5.1 Study-011 - Randomized, Active-Controlled, Double-Blind Trial Evaluating the Safety, in Healthy Infants Given With Routine Pediatric Vaccinations in India.
- 5.3.5.1 Study-3000 - Randomized, Active-Controlled, Double-Blind Trial Evaluating Manufacturing Scale 13vPnC in Healthy Pediatric Subjects.
- 5.3.5.1 Study-3005 - Randomized, Active-Controlled, Double-Blind Trial Evaluating Pilot and Manufacturing Scale 13vPnC in Healthy Pediatric Subjects in the United States.
- 5.3.5.2 Study-3002 - Open-Label 13vPnC Trial in Older Infants and Children Naive to Previous PCV.
- 5.3.5.4 Study-002 - Open-Label, Randomized 13vPnC Trial in Healthy Adults.

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References:

- 1) Quataert SA, Kirch CS, Wiedl LJ, et al. Assignment of weight-based antibody units to a human antipneumococcal standard reference serum, lot 89-S. *Clin Diagn Lab Immunol*. 1995;2(5):590-597.
- 2) World Health Organization. 2005. Pneumococcal conjugate vaccines. Recommendations for the production and control of pneumococcal conjugate vaccines. WHO Tech. Rep. Ser. 927(Annex 2):64–98.
- 3) S. Black, H. Shinefield, B. Fireman, E. Lewis, P. Ray, J.R. Hansen *et al.* and Northern California Kaiser Permanente Vaccine Study Center Group, Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children, *Pediatric Infect Dis J* **19** (2000) (3), pp. 187–195.
- 4) K.L. O'Brien, A.J Swift, J.A Winkelstein, M. Santosham, B. Stover, R. Luddy *et al.* and Pneumococcal Conjugate Vaccine Study Group, Safety and immunogenicity of heptavalent pneumococcal vaccine conjugated to CRM(197) among infants with sickle cell disease, *Pediatrics*.
- 5) K.L. O'Brien, L.H. Moulton, R. Reid, R. Weatherholtz, I. Oski and L. Brown *et al.*, Efficacy and safety of seven-valent conjugate pneumococcal vaccine in American Indian children: group randomised trial, *Lancet* **362** (2003) (9381), pp. 355–361.
- 6) Concepcion NF, Frasch CE. Pneumococcal type 22f polysaccharide absorption improves the specificity of a pneumococcal-polysaccharide enzyme-linked immunosorbent assay. *Clin Diagn Lab Immunol*. 2001 Mar;8(2):266-72.
- 7) Siber GR, Chang I, Baker S, et al. Estimating the protective concentration of antipneumococcal capsular polysaccharide antibodies. *Vaccine*. 2007;25(19):3816-3826.
- 8) Henckaerts I, Goldblatt D, Ashton L, Poolman J. Critical Differences between Pneumococcal Polysaccharide Enzyme-Linked Immunosorbent Assays with and without 22F Inhibition at Low Antibody Concentrations in Pediatric Sera. *Clinical and Vaccine Immunology*, March 2006, p. 356-360, Vol. 13, No. 3

1.2 Pneumococcal OPA:

1.2.1 OPA Principal and Method:

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- 5.3.5.1 Study-004 - Randomized, Double-Blind Trial Comparing 13vPnC in Healthy Infants in the United States
- 5.3.5.1 Study-006 - Randomized, Double-Blind Trial Comparing 13vPnC to 7vPnC in Healthy Pediatric Subjects in Germany.
- 5.3.5.1 Study-500 - Randomized, Double-Blind 13vPnC Trial with Routine Pediatric Vaccination in Italy.
- 5.3.5.1 Study-3008 - Randomized, Double-Blind 13vPnC Trial in Healthy Infants with Routine Pediatric Vaccinations in Canada.
- 5.3.5.1 Study-007 - Randomized, Active-Controlled, Double-Blind Trial Evaluating the Safety, Tolerability, and Immunogenicity in Healthy Infants Given With Routine Pediatric Vaccinations in the United Kingdom".
- 5.3.5.1 Study-008 - Randomized, Active-Controlled, Double-Blind, Trial Evaluating the Safety, Tolerability, and Immunogenicity in Healthy Infants Given With Routine Pediatric Vaccination in France.

2.1.2 ELISA validation strategy:

ICH guidelines are used to validate the Hib ELISA. Validation parameters were Accuracy, Specificity, Linearity, Precision, and Range.

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5.3.1.4 Mening-c-sba: Bioanalytical and Analytical Methods for Human Studies

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Clinical Studies where meningococcal SBA is used:

5.3.5.1 Study-007 - Randomized, Active-Controlled, Double-Blind Trial Evaluating the Safety, Tolerability, and Immunogenicity in Healthy Infants Given With Routine Pediatric Vaccinations in the United Kingdom".

5.3.5.1 Study-501 - Randomized, Double-Blind 13vPnC Trial with Routine Pediatric Vaccination in Spain.

5.3.5.1 Study-3007 - Randomized, Double-Blind 13vPnC Trial with a Meningococcal Conjugate Vaccine and Other Routine Pediatric Vaccinations in Spain.

5.3.5.1 Study-3008 - Randomized, Double-Blind 13vPnC Trial in Healthy Infants with Routine Pediatric Vaccinations in Canada.

2.2.2 SBA validation strategy:

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2.2.3 Comments about SBA assay:

The SBA used in this BLA is properly designed and validated.

3) **---(b)(4)--- ELISA (----(b)(4)-----) used to measure IgG antibodies as part of
---(b)(4)--- toxicity assay.**

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4) Overall recommendations:

Review of the Pneumococcal ELISA, Pneumococcal OPA, *H. influenzae* type B ELISA, and meningococcal SBA assays showed that the assays are appropriate for their intended use and they are properly validated. Thus, the efficacy data are based on results measured by using proper assays.