

Review of Pertussis Assays - July 21, 2009 - Pprevnar 13

- MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Date: July 21, 2009

From: Drusilla Burns, Ph.D.

Through: Milan Blake, Ph.D., Director, DBPAP, OVRR, CBER

To: File/BLA 125324, Biologics License Application submitted by Wyeth Pharmaceuticals Inc. for Pneumococcal 13-Valent Conjugate (Pprevnar plus Diphtheria CRM197 saccharide conjugates for Types 1, 3, 5, 6A, 7F, and 19A) Vaccine, Alum Adsorbed

Subject: Review of pertussis assays used for clinical serology studies

Reference: 1) amendment 0.1 (submitted 10/24/08) section 5.3.1.4. stf-pert-eia-igg and section 5.3.5.1 study 6096A1-004 (pertussis assay serology only)
3) amendment 0.12 (submitted 5/19/09) section 1.11.3 response to 5/8/09 request regarding pertussis ELISAs

INTRODUCTION

Wyeth Pharmaceuticals Inc. submitted a biologics license application (BLA) for their Pneumococcal 13-Valent Conjugate Vaccine. This vaccine is a 13-valent vaccine consisting of Pprevnar plus Diphtheria CRM197 saccharide conjugates for Types 1, 3, 5, 6A, 7F, and 19A. The pneumococcal polysaccharide conjugates are adsorbed to aluminum adjuvant. Wyeth is seeking an indication for active immunization in infants and young children against invasive disease and otitis media caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. Because this vaccine would be expected to be given concomitantly with vaccines containing pertussis antigens, Wyeth conducted clinical studies to assess the effect of vaccination with 13-valent Pneumococcal Conjugate Vaccine (13vPnC) compared to a 7-valent Pneumococcal Conjugate Vaccine (7vPnC, Pprevnar) on antibody responses to pertussis antigens when

given concomitantly with a pertussis-containing vaccine. The pivotal clinical study for concomitant vaccination with a pertussis-containing vaccine is Study 6096A1-004 in which 13vPnC or 7vPnC was given concomitantly with Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined (Pediarix).

FOCUS OF REVIEW

The focus of this review is the pertussis assays used to measure pertussis immunogenicity in studies to assess concomitant vaccination of 13-valent Pneumococcal Conjugate Vaccine with a pertussis-containing vaccine. These assays were conducted at the -----
------(b)(4)-----.

REVIEWER'S CONCLUSIONS

Based on my review, I consider the pertussis ELISA assays performed at --(b)(4)-- to be sufficiently validated for their intended purpose as used in the pivotal clinical study, 6096A1-004.

REVIEW OF PERTUSSIS ASSAYS:

Much of the pertussis assay validation data for PT, FHA, and PRN ELISAs was reviewed under IND --(b)(4)-- as indicated on p. 4 of section 1.6.3 (Correspondence Regarding Meetings) of the BLA. Items reviewed under IND --(b)(4)-- pertaining to pertussis ELISA validation include information on assay accuracy, repeatability, intermediate precision, assay range, limit of quantitation, system suitability parameters, dilutional linearity, purity of coating antigens (PT, FHA, and PRN), as well as description of the ELISA methods, description of the calculation methods, and assay control charts. During review of the IND, several communications occurred between CBER and Wyeth to address CBER questions and concerns about the information provided in the IND. Wyeth satisfactorily addressed these concerns and the assays were determined to be adequate for the intended purposes as used in clinical study 6096A1-004. Wyeth was informed by CBER in a telecon on June 30, 2008 that CBER judged the assays to be suitable for use for evaluation of pertussis antibody responses in clinical study 6096A1-004.

Subsequently, the assays for that pivotal study were performed. Those assay results are included in the BLA submission, as is a summary of the validation data for the PT, FHA, and PRN assays. This assay validation summary contains information on specificity, coating antigen purity specifications, assay linearity, dilutional linearity, accuracy, precision, range, lower limit of quantitation.

Limited information was submitted in the BLA pertaining to the FIM ELISA which was not reviewed under IND --(b)(4)--. The FIM ELISA was used in two supportive (non-pivotal)

clinical studies, 6096A1-3008 and 6096A1-007, but was not used for the pivotal study 6096A1-004 since the pertussis vaccine used for that study did not contain pertussis fimbriae. The information submitted in regards to the FIM assay in the BLA was not sufficient to determine whether the assay is adequate for the purposes for which it was used in those studies. I conveyed this concern via e-mail on April 16, 2009 to Julianne Vaillancourt, Chair of the BLA Review Committee and Tina Khoie, the clinical reviewer for the BLA. In my opinion, the fimbriae serology from these non-pivotal studies should not be considered when drawing conclusions concerning concomitant vaccination of 13vPnC vaccine with pertussis vaccines.

While issues regarding PT/FHA/PRN assay validation were resolved during IND review, I noted one new issue in the review of the information submitted in the BLA in regards to purity of the coating antigens used in the pertussis assays that could affect use of the pertussis ELISAs for future studies. CBER conveyed this issue (elaborated below) to Wyeth on May 8, 2009.

We note that on April 9, 2008, you submitted information to IND--(b)(4)- documenting adequate purity of the PT, FHA, and PRN coating antigens used in the pertussis ELISAs conducted for study 6096A1-004. However, in reviewing the information in your amendment to the BLA dated October 24, 2008 regarding the pertussis ELISAs, we note that on p. 5 of section 5.3.1.4-Pert EIA IgG, you indicate that specifications for the pertussis ELISA coating antigens are "antigens were accepted if their purity met the following pre-determined purity limits:-(b)(4) PRN, -(b)(4) PT, (b)(4) FHA, and -(b)(4)- FIM." These specifications are not adequate to insure specificity of the assay if used for future studies. If the pertussis assays are to be used for future studies, these specifications should be amended appropriately. Please acknowledge.

In their submission of May 18, 2009, Wyeth acknowledged this comment.

ADEQUACY OF ASSAYS TO SUPPORT CLINICAL ENDPOINTS

Pivotal Study 6096A1-004

Study 6096A1-004 is considered the pivotal study for analysis of concomitant administration of 13vPnC with a pertussis-containing vaccine given to infants. The study was conducted in the U.S. using Pediarix (a U.S. licensed pertussis-containing vaccine) given at 2, 4, and 6 months of age. In regards to pertussis immunogenicity analysis, two analyses were used in this study. The primary endpoint was the proportion of subjects achieving a specified antibody level for each pertussis antigen. The defined levels were based on the observed values achieved by 95% of the subjects in the 7vPnC group which were 40.5 EU/ml, 16.5 EU/ml, and 26 EU/ml for FHA, PT, and PRN, respectively. An additional analysis was conducted in which the geometric mean concentrations (GMCs) for the 13vPnC and the 7vPnC group were compared. The lower limits of the 95% CIs for the geometric mean ratio (GMR) exceeded a 0.67 (1.5-fold) criterion for each of the pertussis antigens (PT, FHA, PRN). After reviewing the information provided concerning the PT, FHA and PRN assays, I

believe that the precision, accuracy, limit of quantitation, specificity and linearity of these assays are adequate to support these analyses.

Other Studies

Pertussis-containing vaccines were given to infants in a number of other clinical studies submitted in this BLA. They were:

Study 6096A1-3008 (Canada):

Pertussis-containing vaccine used: Pentacel (U.S. licensed)

Schedule for pertussis vaccine: 2,4, and 6 months of age

Assays used: PT, FHA, PRN, FIM ELISAs

Analyses conducted:

PT, FHA, PRN \geq 5 EU/ml; FIM (2 and 3) \geq 2.2 EU/ml

The lower limit of the 95% CI for the ratio of GMCs (13vPnC versus 7vPnC) was > 0.5

FHA \geq 7.82 EU/ml

PT \geq 12 EU/ml; FHA \geq 20 EU/ml; PRN \geq 7 EU/ml; and FIM \geq 4 EU/ml (values obtained by 95% of the 7vPnC group after the infant series)

Study 6096A1-500 (Italy)

Pertussis-containing vaccine used: Infanrix hexa

Schedule for pertussis vaccine: 3, 5, and 11 months of age

Assays used: PT, FHA, PRN ELISAs

Analyses conducted:

PT, FHA, PRN \geq 5 EU/ml

Geometric mean ratios (GMR) for 13vPnC versus 7vPnC Group

PT \geq 16 EU/ml; FHA \geq 31 EU/ml; PRN \geq 40 EU/ml (values obtained by 95% of the 7vPnC group after the infant series)

Study 6096A1-501(Spain)

Pertussis-containing vaccine used: Infanrix hexa

Schedule for pertussis vaccine: 2, 4, and 6 months of age

Assays used: PT, FHA, PRN ELISAs

Analyses conducted:

PT, FHA, PRN ³ 5 EU/ml

Geometric mean ratios (GMR) for 13vPnC versus 7vPnC Group

FHA ³ 7.82 EU/ml

PT ³ 20 EU/ml; FHA ³ 64 EU/ml; PRN ³ 39 EU/ml (values obtained by 95% of the 7vPnC group after the infant series)

Study 6096A1-007(United Kingdom)

Pertussis-containing vaccine used: Pediacel

Schedule for pertussis vaccine: 2, 3, and 4 months of age

Assays used: PT, FHA, PRN, FIM ELISAs

Analyses conducted:

PT, FHA, PRN ³ 5 EU/ml; FIM (2 and 3) ³ 2.2 EU/ml

Geometric mean ratios (GMR) for 13vPnC versus 7vPnC Group

FHA ³ 7.82 EU/ml

PT ³ 17 EU/ml; FHA ³ 20 EU/ml; PRN ³ 15 EU/ml; FIM ³ 5 EU/ml (values obtained by 95% of the 7vPnC group after the infant series)

Note: The pertussis-containing vaccine used in this trial (Pediacel) was not given on the U.S schedule of 2, 4, and 6 months, instead it was given at 2, 3, and 4 months. While the difference between groups (13vPnC-7vPnC) for the PRN antigen at the level achieved by 95% of the 7vPnC subjects was -3.1% with a lower limit of -10.0% (with the specified lower limit for non-inferiority being ³ 10%), the significance of this difference for the U.S. population is difficult to interpret because of the difference in schedule employed in the trial.

Study 6096A1-008 (France)

Pertussis-containing vaccine used: (Pentavac)

Schedule for pertussis vaccine: 2, 3, 4, and 12 months of age

Assays used: PT, FHA ELISAs

Analyses conducted

PT, FHA, PRN ³ 5 EU/ml

Geometric mean ratios (GMR) for 13vPnC versus 7vPnC Group

FHA ³ 7.82 EU/ml

PT ³ 26 EU/ml; FHA ³ 36 EU/ml; (values obtained by 95% of the 7vPnC group after the infant series)

Review Comments concerning the pertussis ELISAs:

- The PT, FHA, and PRN ELISAs performed at --(b)(4)--are sufficiently validated for their intended purpose as used in the pivotal clinical study, 6096A1-004.
- The FIM ELISA was used for supportive, but non-pivotal studies 6096A1-3008 and 6096A1-007. The FIM ELISA was not demonstrated to be adequately validated and therefore, results from that assay cannot be interpreted.

Endpoints used in many of the supportive, but non-pivotal trials, to evaluate pertussis responses included the proportion of subjects with antibody level ³ 5 EU/ml for PT, FHA, and PRN or ³7.82 for FHA. These antibody concentrations are near, or even slightly below, the lower limit of quantitation (LLOQ) for the ELISAs. Thus, a very high proportion of subjects (approaching 100%) should achieve these levels after a 3-dose infant series. Moreover, because these concentrations are in the lower, more variable range of the assay, false positives could occur simply due to assay variability. Thus, these endpoint definitions have low sensitivity for detecting differences between the 7vPnC and 13vPnC groups and therefore are not particularly meaningful endpoints. Endpoint definitions based on values obtained by 95% of the 7vPnC group or on geometric mean ratios of the GMCs are more meaningful.