Review of Amendments 8,9, and 10 - KINRIX

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research
Date: December 13, 2007
From: Drusilla Burns, Ph.D., Chief, LRSP, DBPAP, OVRR
Through: Milan Blake, Ph.D., Acting Director, DBPAP, OVRR
Subject: Review of Amendments 8,9, and 10 of BLA 125260, DTaP-IPV from GlaxoSmithKline (GSK)
To: File

I have reviewed BLA 125260/0.8, 125260/0.9 and 125260/0.10 submitted September 24, 2007, October 30, 2007, and November 13, 2007 respectively. These submissions contained responses from GSK to my questions raised in my review of 125260/0 and 125260.3 dated August 27, 2007. Below are the issues that I raised in my review of August 27, 2007 and my assessment of GSK's responses to these questions and comments. As indicated below, GSK adequately responded to each of my concerns.

Product and manufacturing issues:

Final container stability

24-month stability data are available for the three clinical consistency lots used in the Phase III study. These lots differ from commercial lots in that they were formulated at pilot scale. The commercial demonstration lots have been placed on stability and will be followed for 36 months, the proposed dating period. GSK previously submitted a comparability protocol for demonstrating that the commercial-scale lots were comparable to those lots used in the pivotal clinical study. CBER agreed that the proposal for bridging the commercial and clinical manufacturing facilities is satisfactory. One of the components of that comparability protocol is that "Results for the commercial scale lots will be compared to results obtained for the three clinical consistency lots. To be considered acceptable/validated, results for the commercial scale lots must be within the historical range obtained with the clinic-scale product". However this criterion was not strictly met.

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Additional stability data for the commercial lots may shed light on whether these discrepancies are only due to variability of the test.

COMMENT CONVEYED TO GSK:

- Please provide any updated stability data that you might have for the commercial demonstration lots ----------.
  Assessment of GSK's response:
  In their submission of October 30, 2007 (Amendment 9), GSK provided 6 month stability data for ---------- (syringes), ---------- (vials), and ---------- (vials). All potency test stability data for all pertussis antigens were within the ranges shown above for the clinical consistency lots with the exception of the 6-month value for pertactin potency for ---------- (syringes). However, pertactin potency values for this lot are well within the established specifications. Moreover, they are within values obtained in the stability analysis of the clinical consistency lots. Therefore, I do not have concerns.
  When the stability data for the phase III clinical lots were reviewed (Section 3.2.P.8.3), the following were noted.
  1. Potency for pertussis antigens at the 24-month time point was somewhat lower than that observed at earlier time points. Additional stability data might add insight into whether this represents a real downward trend or whether this represents variability of the test.

  COMMENT CONVEYED TO GSK:
- Please provide any updated stability data that you might have for the phase III clinical consistency lots DC20A001, DC20A002, and DC20A003.
  Assessment of GSK's response:
  In their submission of September 24, 2007 (Amendment 8), GSK provided updated stability data for these lots demonstrating the absence of any downward trend in the potency of the pertussis antigens.

Pertussis Serology

Pertussis ELISAs

Study DTaP-IPV-048

ELISA validation reports for pertussis assays conducted by GSK were submitted in the application. Certain additional information is needed to confirm that the assays are performing in a manner such that the data produced are meaningful and support GSK's conclusions.

COMMENTS:

- Please submit data which support the precision and accuracy of the assay for samples at or near the lower limit of quantitiation and at or near the cut-off values of ≥ 5 EU/ml.
- Please submit data which support the precision of the assays over their entire working ranges.
- For each critical reagent used in the pertussis ELISAs, please submit a summary of the data generated to qualify the batch(es) used in the critical assays presented in this submission.
- Please provide data that demonstrate that the pertussis assay ELISA assays behaved in a stable manner and that critical assay parameters did not change from the time that the assays were validated (ELISA validation reports are dated 1998) until the time that critical assays presented in this submission were conducted.
  Assessment of GSK's response:
  In their submission of November 13, 2007 (Amendment 10), GSK provided the requested information which adequately addresses my concerns.
  Study DTaP-IPV-047

Pertussis immunogencity data generated in a phase II study (DTaP-IPV-047) were submitted in this application. GSK considers the immunogenicity data generated in this trial to be supportive. The pertussis ELISA assays used to evaluate the clinical samples from this trial were assayed in the ---------- GSK submitted pertussis assay validation reports for the ------ ---------- in amendment 0.3. I found the validation report to be missing critical information such that the validity and soundness of the data generated using these assays cannot be evaluated. Without this information, I do not consider the pertussis immunogenicity data from this study to be supportive.

COMMENTS CONVEYED TO GSK:

1. The validation reports received for the pertussis ELISA conducted in the ---------- ---------- are missing critical information that would justify the use of these assays. Without this information, pertussis immunogenicity data from Study DTaP-IPV-047 will not be considered supportive. The following information is needed to complete the validation study report for each pertussis antigen:
   - A detailed description of the methods and software used to calculate ELISA units/ml in each test sample and representative calculations
   - A detailed description of each of the critical reagents
   - The specifications for each critical reagent
   - For each critical reagent, a summary of the data generated to qualify the batch(es) used in the critical assays presented in this submission
   - For each coating antigen, the source, a summary of the purification process (if available) and any testing to ensure purity (i.e. absence of other vaccine antigens)
   - Details describing how the --------- pertussis reference serum was calibrated against FDA control serum lot #3
   - Data demonstrating the assay has acceptable precision and accuracy over the entire working range
   - Data supporting the precision and accuracy of the assay for samples at or near the lower limit of quantitation and at or near the assigned cut-off value of 5 EU/ml
   - Data demonstrating specificity of the assay
2. Dilutional linearity studies for each of the pertussis antigen ELISAs shows considerable bias as the sample is diluted. Such a large bias might affect interpretation of the data generated by these assays. Please comment.
3. Please provide data that demonstrate that the pertussis assay ELISA assays behaved in a stable manner and that critical assay parameters did not change from the time that the assays were validated until the time that critical assays presented in this submission were conducted.

Assessment of GSK's responses:

In their submission of November 13, 2007, GSK responded that they no longer use the ---------- for serological testing. They further indicated, as they discussed with CBER during the September 18, 2007 teleconference, that they do not consider the immunogencity data obtained in Study 047 to be pivotal for licensure of the DTaP-IPV vaccine. Therefore, they propose the responses to the comments above should not be required as these data need not be considered by CBER for licensure. I have confirmed with Dr. Karen Farizo, the clinical reviewer on this file, that CBER will not consider immunogenicity data from Study 047 for licensure. Therefore, GSK's response is adequate.

Clinical Serology Results

The pivotal phase III study submitted to support the requested indication for the vaccine was DTaP-IPV-048. This was an open (double-blind for consistency lots), randomized, multicenter clinical trial of the safety, immunogenicity, and consistency of three manufacturing lots of GSK's DTaP-IPV candidate vaccine compared to that of separate injections of GSK's DTaP vaccine (Infanrix) and Aventis Pasteur's IPV vaccine (IPOL) administered as a booster dose in healthy children 4 to 6 years of age. In regards to pertussis immunogencity, the study objectives were:

Primary objectives:

- To demonstrate the lot-to-lot consistency of three manufacturing lots of DTaP-IPV vaccine in terms of pertussis toxoid (PT), filamentous hemaglutinin (FHA), and pertactin (PRN) geometric mean concentrations (GMCs) in a subset of subjects one month after vaccination

  Criteria for lot consistency:

  For each pair of lots and for each antigen, the lower and upper limits of the 95% CI on the GMC ratio were within the pre-defined limits [0.67, 1.5].
- To demonstrate the non-inferiority of DTaP-IPV vaccine compared to Infanrix + IPOL administered separately in terms of booster responses

  Criteria for non-inferiority of DTaP-IPV vaccine (1 month after vaccination)

  For each antigen, the upper limit of the two-sided standardized asymptotic 95% CI for the difference between the Infanrix + IPOL group and (minus) the DTaP-IPV group in the percentage of subjects with a booster response was less than or equal to the pre-defined clinical limit of 10%

  For pertussis antigens, a booster response is defined as
  - Initially seronegative subjects (pre-booster antibody concentration below cut-off of <5 EU/ml) with an increase of at least four times the cut-off one month after vaccination (post-booster antibody concentration ≥20 EU/ml
  - Initially seronpositive subjects with pre-booster antibody concentration ≥5 EU/ml and <20 EU/ml with an increase of at least four time the pre-booster antibody concentration one month after vaccination
  - Initially seropositive subjects with pre-booster antibody concentration ≥20 EU/ml with an increase of at least two time the pre-booster antibody concentration one month after vaccination

Secondary Objectives

- To evaluate the lot-to-lot consistency of three manufacturing lots of DTaP-IPV vaccine in terms of pertussis booster responses one month after vaccination
- To evaluate DTaP-IPV vaccine compared to Infanrix+IPOL administered separately in terms of pertussis GMCs one month after vaccination

  GSK also performed a secondary analysis in which they examined what they call "seropositivity status" which they define as
- Anti-PT ≥5 EU/ml
- Anti-FHA ≥5 EU/ml
- Anti-PRN ≥5 EU/ml

  GSK met their primary and secondary objectives as far as immunogenicity of the pertussis components is concerned, however the additional analysis in which they look at rates of seropositivity is uninformative because their cut-off value for seropositivity is

near, or only slightly above, the lower limit of quantitation (LLOQ) for the pertussis ELISA's. Thus, a very high proportion of subjects had titers above the cut-off level even before the vaccination that occurred during the trial (see Table 22 on p. 8 and Table 30 on p. 11 of this review). Furthermore, because the cut-off values are in the lower, more variable range of the assay, false positives may occur due solely to assay variability. Thus this analysis has an unacceptably low sensitivity and should not be considered.

COMMENT CONVEYED TO GSK:

We note that you conducted additional analyses in which you determined seropositivity status (ELISA values for pertussis antigens ≥5 EU/ml). We note that the cut-off values that you used are near, or only slightly above the LLOQs for the assays. These cut-off values are in the lower, more variable range of the assays such that false positives may occur solely due to assay variability. We also note that a large proportion of titers obtained pre-vaccination were at or above these levels. Thus, seropositivity is an insensitive method for evaluating differences between DTaP-IPV lots or between separate versus combined vaccines. Therefore, CBER considers seropositivity data to be uninformative and will not be considered as supportive. Please comment.

Assessment of GSK's response:

In their submission of November 13, 2007 (Amendment 10), GSK acknowledged CBER's position regarding the use of seropositivity as part of the booster response.