Final Review Memo - KINRIX

MEMORANDUM
DEPARTMENT OF HEALTH & HUMAN SERVICES
FDA/CBER/OVRR/DBPAP
Date: 12/18/2007
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To: File
Subject: Final Review Memo
GSK DTaP-IPV (Kinrix) BLA STN 125260/0.0, 125260/0.3 and 125260/0.10
Diphtheria and Tetanus Serology

SUMMARY

In support of the BLA for DTaP-IPV (Kinrix) GlaxoSmithKline Biologics (GSK) submitted the standard operating procedures (SOPs) and the validation reports for the Tetanus, Diphtheria and Pertussis ELISAs and the poliovirus neutralization assay that were used to assess the immunogenicity of DTaP-IPV in two controlled clinical studies (DTaP-047 and DTaP-048). This review memo focuses specifically on the Diphtheria and Tetanus serology reports provided.

The primary serological objective of the phase II trial (DTaP-IPV-047) was to evaluate the DTaP-IPV vaccine as compared to DTaP and IPV vaccines administered separately in terms of diphtheria (D), tetanus toxoid (T) booster responses one month after vaccination when co-administered with MMR vaccine. For DT the criteria for non-inferiority one month after DTaP-IPV + MMR dose was the upper limit of the standardized two-sided 95% confidence interval (CI) for the groups DTaP + IPV + MMR minus DTaP-IPV + MMR in boost response rates of ≤ 10% for DT. The secondary objective of study DTaP-IPV-047 was to evaluate DTaP-IPV vaccine as compared to DTaP and IPV vaccines administered separately in terms of DT geometric mean concentrations (GMCs) one month after vaccination.

For the pivotal phase III trial (DTaP-IPV-048) the co-primary serological objectives were to demonstrate lot-to-lot consistency of three manufacturing lots of DTaP-IPV vaccine in terms of DT GMCs in a subset of subjects 1 month after vaccination when co-administered with MMR and to demonstrate the non-inferiority of the DTaP-IPV vaccine compared to Infanrix® + IPOL® administered separately in terms of D and T booster responses in a subset of subjects one month after vaccination when co-administered with M-M-R®II. The criteria for lot-to-lot consistency were that the lower and upper limits of the 95% CI of GMC/GMT ratios were within the pre-defined clinical limits of 0.67 and 1.5. For the non-inferiority of DTaP-IPV vaccine one month after boost vaccination, the D and T criteria were that the upper limit of the two-sided standardized asymptotic 95% CI for the difference between the Infanrix® + IPOL® group minus the DTaP-IPV groups in the percentage of subjects with a booster response were less than or equal to the pre-defined clinical limit of 10%. Secondary objectives of this study were to evaluate the lot-to-lot consistency of 3 manufacturing lots of DTaP-IPV vaccine in terms of D and T booster responses one month after vaccination and to evaluate DTaP-IPV vaccine

compared to Infanrix® + IPOL® administered separately in terms of D and T booster responses one month after vaccination.

In both clinical studies DTaP-IPV-047 and DTaP-IPV-048 anti-D and anti-T booster responses were defined as initially seronegative subjects (pre-booster antibody concentration below a cut-off of < 0.1 IU/ml) with an increase of at least four times the cut-off one month after vaccination (post-booster antibody concentration ≥ 0.4 IU/ml) and initially seropositive subjects (pre-booster antibody concentration ≥ 0.1 IU/ml) with an increase of at least four times the pre-booster antibody concentrations one month after vaccination. All D and T antibody concentrations were determined by ELISA with assays supportive of study DTaP-IPV-047 performed at ---------- and those supportive of study DTaP-IPV-048 performed at GSK Biologicals laboratories in Rixensart, Belgium. For both D and T it is believed that antibody level < 0.01 IU/ml indicate susceptibility to the toxin, that levels between 0.01 and 0.1 IU/ml confer basic protection against toxin-mediated disease and that antibody concentrations ≥ 0.1 IU/ml confer full protection.

In the original submission (125260/0.0) GSK provided SOP and validation reports for the Diphtheria and Tetanus ELISAs performed at GSK laboratories in Rixensart, Belgium; however, no validation or SOPs were provided for those assays carried out at ----------. On May 18, 2007 CBER requested the serological assay validation packages for the assays runs at ---------- to support the phase II study (DTaP-IPV-047) and received the requested serological validation packages on July 3, 2007 (125260/0.3).

Review of the ---------- serological packages provided for D and T ELISAs were considered not to contain sufficient information to accurately assess the data. Specifically the following information was not provided: the concentration of D and T antigens used for plate coating, the concentrations of the low, medium and high positive human control sera samples, the linear range of the plate reader used, what the GMCs of the working reference sera and positive control sera were, how critical reagents such as the reference sera, antigen and secondary reagent were qualified for use in the assay and a more detailed description of how GMCs were calculated with an examples of these calculations. Furthermore, no data was submitted to indicate the specific GMC range of samples used to determine assay precision and no examination of assay specificity was performed. With respect to parallelism of both ELISAs the acceptable slope ranges were considered quite broad (1.56 to 2.10 for the Diphtheria ELISA and 1.63 to 2.03 for the Tetanus ELISA) which could affect the interpretation of the data. Finally, the dilutional linearity data provided for both the Diphtheria and Tetanus showed significant variability at both high and low dilutions for the Diphtheria ELISA and a bias at low dilutions for the Tetanus ELISA.

SOPs and validation reports for the Diphtheria and Tetanus ELISAs conducted at GSK Biologics, Rixensart, Belgium in support of the phase III trial (DTaP-IPV-048) were provided in the original BLA submission. After review of these serological packages, additional information was also considered to be required to assure that the data obtained from these ELISA assays were meaningful and supportive of GSK's conclusions with respect to immunogenicity. Specifically the following data was required:

1. SOPs for "Qualification of new lots of reference and control sera for use in ELISAs" and "Qualification of new lots of antigen and detection reagents for use in ELISAs".
2. Data specific to the qualification of batches of the critical reagents used in these assays.
3. Data which indicates the specific GMC range of samples used to determine assay precision and dilutional linearity.
4. Updated validation reports (those submitted in the original BLA application were dated 28/5/99 and September 1998, respectively for the Diphtheria and Tetanus ELISAs) which provide data to indicate that the assays are performing in a stable manner and that the critical assay parameters (i.e., precision, accuracy, linearity and parallelism) had not changed since the time of the validation reports provided.

CBER's comments regarding the Diphtheria, Tetanus and Pertussis serological methods provided in 125260/0.0 and 125260/0.3 were relayed to GSK on September 13, 2007 and are listed below.

CBER Comments and Questions for DTaP-IPV; STN:125260

Phase II Clinical Trial (DTaP-IPV-047)

1. At this time, the validation reports for the Diphtheria, Tetanus and Pertussis ELISAs conducted at ---------- are missing critical information such that the validity and soundness of the data generated using these assays cannot be evaluated. A considerable amount of addition information and data are needed to demonstrate that the assays are appropriately validated. Examples of critical information and data that are missing from the reports are provided below.
    a. A detailed description of each of the critical reagents which should include the source of each reagent, the specifications for each reagent and for each reagent a summary of the data used to qualify the batch(es) of reagents employed in the critical assays presented in this submission.
    b. For each coating antigen, the source, a summary of the purification process (if available), any testing done to ensure purity (i.e., absence of other vaccine antigens) and the coating concentration of each antigen.
    c. Greater detail on how the -------- working reference standards and quality control sera were calibrated against international or FDA reference standards and what the GMCs/GMTs of the working reference sera and positive control sera are.
    d. A detailed description of the methods and software used to calculate GMCs/GMTs in each test sample. Representative calculations should also be provided.
    e. Data indicating that each ELISA assay has acceptable precision and accuracy over the entire working range. This data should include the specific GMC/GMT range of the samples used to determine assay precision.
    f. For the Pertussis ELISAs, 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.
    g. Data demonstrating the specificity of each ELISA assay.
2. The dilutional linearity studies for each of the Pertussis antigen ELISAs as well as the Diphtheria ELISA shows considerable bias as samples are diluted. Such a bias might affect interpretation of the data generated by these assay. Please comment.

3. For parallelism in the Diphtheria and Tetanus ELISAs, the acceptable slope ranges are very broad (1.56 to 2.10 for the Diphtheria ELISA and 1.63 to 2.03 for the Tetanus ELISA) and could affect the interpretation of the data. Please comment.
4. Please provide data that demonstrate that the Diphtheria, Tetanus and Pertussis ELISA assay behave in a stable manner and that the critical assay parameters (i.e., precision, accuracy, linearity and parallelism) did not change from the time that the assays were validated until the time that the assays presented in this submission were conducted.

Phase III Clinical Trial (DTaP-IPV-048)

1. Please submit the SOPs for "Qualification of new lots of reference and control sera for use in ELISAs" and "Qualification of new lots of antigen and detection reagents for use in ELISAs". For each critical reagent used in the Diphtheria, Tetanus and Pertussis ELISAs, please submit a summary of the data generated to qualify the batch(es) used in the assays presented in this submission.
2. Please submit data which supports the precision of the Diphtheria, Tetanus and Pertussis ELISAs over their entire working ranges and indicate the specific GMC/GMT range of samples used to determine assay precision.
3. For the Pertussis ELISAs, please submit data which supports the precision and accuracy of the assay for samples at or near the lower limit of quantitation and at or near the cut-off values of ≥ 5 EU/ml.
4. The validation reports submitted in this application are dated 28/5/99 for the Diphtheria ELISA and September 1998 for the Tetanus and Pertussis ELISA assays. Please provide data which indicates that the assays perform in a stable manner and that the critical assay parameters (i.e., precision, accuracy, linearity and parallelism) have not change from the time the assays presented in this submission were conducted.

GSK's responses to CBER's comments on serology test methods were received November 13, 2007 (125260/0.10) and are listed below.

Phase II Clinical Trial (DTaP-IPV-047)

With regard to the comments 1-4 related to the phase II clinical trial (DTaP-IPV-047), GSK indicated that they no longer use ---------- for serological testing. GSK also indicated that they did ***not*** consider the diphtheria and tetanus immunogenicity data obtained in trial DTaP-IPV-047 pivotal for licensure of the candidate vaccine with which Dr. Karen Farizo, the CBER clinical reviewer on this BLA, concurred. For these reasons, GSK proposed that the responses to CBER's comments for study DTaP-IPV-047 were not required as the data need not be considered by CBER for licensure.

RECOMMENDATION:

With regard to the Diphtheria and Tetanus serology comments raised in review of 125260/0.0 and 125260/0.3 GSK's responses and the data provided (125260/0.10) are considered adequate. Based on the information provided, the Diphtheria and Tetanus ELISAs used to evaluate the immunogenicity of DTaP-IPV for the phase III clinical trial are acceptable and there are no outstanding concerns.